Abstract

Synthesis of Amides and Amines via Catalytic Activation of Alcohols using Ruthenium and Iridium Complexes

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The research described in this thesis covers the development of new eco-friendly and atom-economic synthetic methods for C–N bond formation based on the transition-metal-catalyzed activation of alcohol. This study focused on the synthesis of synthetically and industrially valuable molecules such as amides and amines. Along with the great importance of the alcohol activation strategy, the

basic concepts and the corresponding state-of-the-art reactions are explained in Chapter 1. Efficient synthesis of amides from alcohols and azides, a new alternative nitrogen source, using the alcohol activation strategy is described in Chapter 2. The amide synthetic method utilizing stable, easy-to-handle, and readily available starting materials is highly desirable. Our developed method presents the first example of amide synthesis starting from alcohols and azides via the Ru-catalyzed dehydrogenation of alcohol-*in situ* reduction of azides. Amides and secondary amines were synthesized from esters and primary amines for the first time using a commercially available Ir catalytic system as described in Chapter 3. Two important C–N bonds were obtained in one-pot sequential reactions via amidation and borrowing-hydrogen method. This method provides an efficient way to utilize an ester group using the removed alcohol as the next carbon source after the amidation. These synthetic protocols generate hydrogen or water as the non-harmful by-products, satisfying the concept of sustainable chemistry. The developed methods expand the synthetic versatility and efficiency of amide and amine bond formation.

Keywords: alcohol activation, dehydrogenation, borrowing-hydrogen, transition metal catalyst, C-N bond formation

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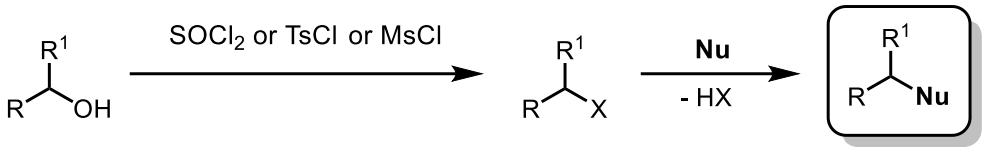
Chapter 1. Dehydrogenative Alcohol Activation

1.1 Introduction

As the global economy has grown over a century, large amounts of energy supplies are needed to maintain the current high technologies and support the production capacity. In fact, we mainly depend on fossil fuels, including oil, natural gas, and coal, and the finite reserves of these fossil fuels have resulted in a constant increase in their cost. Furthermore, to avoid the adverse impact on the environment caused by burning the fuel, it is an urgent task to develop sustainable energy supplies. Biomass is a potential solution to this environmental problem because it is naturally abundant and a renewable resource. The available biomass for industrial synthesis includes agricultural residues and wood wastes. Wood waste contains lignocellulose, which is transformed to lignose oil, and finally highly functionalized alcohols are obtained. In this regard, a growing interest in chemical synthesis is to utilize these alcohols as the starting materials. This chapter covers the reactions using alcohols as a carbonyl source from conventional methods to transition-metal-catalyzed transformations.

1.2 Conventional and potential reactivity of alcohols

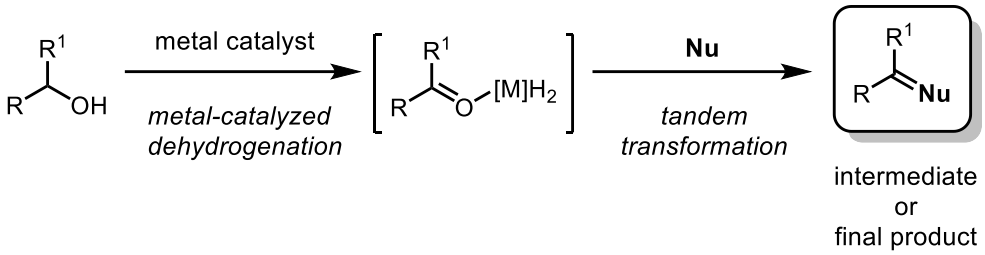
Alcohols are valuable building blocks in chemical synthesis because they are widely available and stable compounds. They are produced by the pyrolysis of biomass, one of the most important renewable resources. The direct use of alcohols in organic synthesis, especially for C–C and C–N bond-forming reactions, is taking the center stage in current organic synthesis. In general, to utilize alcohols as a C-source, the OH group is transformed into a good leaving group. The strategies for this transformation include the protonation of alcohol for enhancing the reactivity under acidic conditions. Although this strategy is environmentally friendly as it generates only water as the by-product, the applicable nucleophiles are severely limited to one type of strong nucleophile in acidic media. Amines are not suitable nucleophiles under this condition. Other strategies involve the transformation of alcohols to the corresponding halides or tosylates prior to the reaction (Scheme 1.1). However, these methods limit the sustainability of the reaction because they generate stoichiometric amounts of chemical waste, and the toxicity of removed halides cause environmental problems.



X = Cl, OTs, OMs

Scheme 1.1 Conventional alcohol functionalization strategy

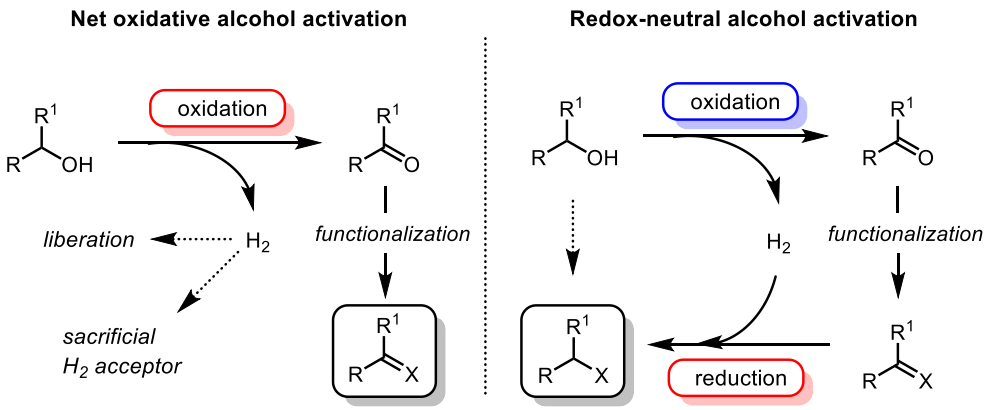
Development of efficient methods for the activation of alcohol and nucleophilic functionalization of bonds have high demand and are challenging in all branches of organic synthesis[1]. As a greener alternative, a combination of TEMPO catalyst and sodium hypochlorite has been developed for the dehydrogenation of alcohols. However, this method suffers from the need for a stoichiometric amount of sodium hypochlorite, a co-catalyst, and the use of chlorinated solvents, producing an equivalent amount of sodium chloride[2]. Transition-metal-catalyzed alcohol activation via direct alcohol dehydrogenation has attracted considerable attention as a highly efficient alternative for the conventional method. In the presence of a suitable metal catalyst, the removal of a hydrogen molecule from an alcohol generates the corresponding carbonyl that is more reactive than the alcohol and thus easily undergoes tandem functionalization with various nucleophiles including amines (Scheme 1.2).



Scheme 1.2 Dehydrogenative functionalization of alcohols

The reactions based on the activation of alcohol using transition metals can be categorized into two types according to the mechanism: redox-neutral or net oxidative alcohol activation[3]. The two mechanisms differ depending on the net oxidation state of participating molecules. Commonly, the metal-catalyzed removal of a hydrogen molecule from an alcohol produces the corresponding activated carbonyl compound. Then, if the removed dihydrogen is used for the reduction of other unsaturated molecules participating in the reaction, the mechanism is known to be redox-neutral, but if the removed dihydrogen is released from the reaction media or transferred to a sacrificial hydrogen acceptor, the mechanism is known as oxidative alcohol activation (Scheme 1.3). In both the mechanisms, no external oxidant or reductant is required[4], and hydrogen is the sole by-product, a clean energy source. Redox economy is very important in sustainable chemistry. This new

bond-formation concept involving the internal exchange of oxidation state between an alcohol and other functional groups will provide great alternatives to the existing methods.



Scheme 1.3 Mechanistic classification of alcohol activation

1.3 Amide bond synthesis

1.3.1 Introduction

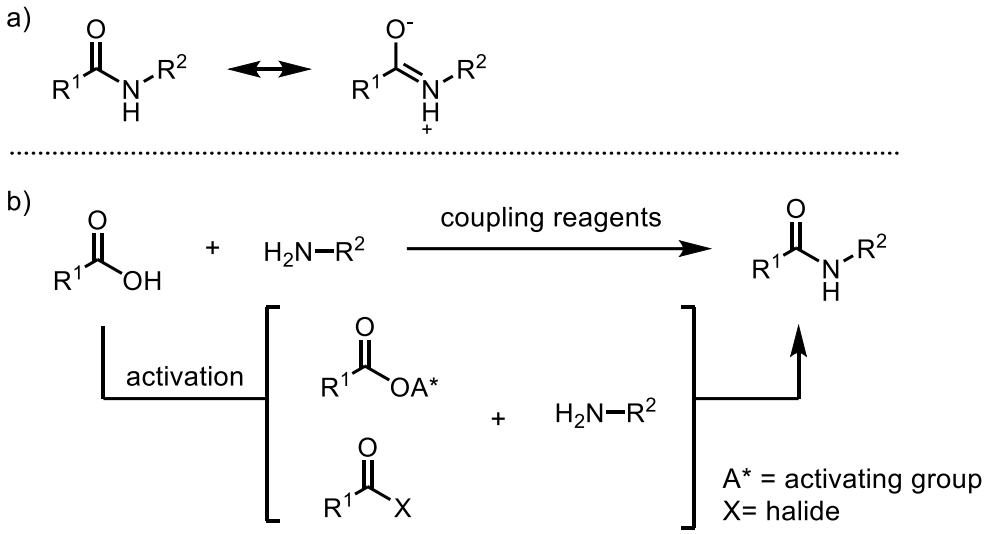
Given the advantages of using an alcohol as the carbon source for a new bond formation, transition-metal-catalyzed dehydrogenative amide bond formation methods have emerged as a greener alternative to traditional amide synthesis. In this protocol, the hydrogen gas generated from an alcohol is released or transferred to a sacrificial hydrogen acceptor, resulting in the net oxidation of

the final product. Using a metal catalyst, a stable substrate, an alcohol, is converted to a more reactive carbonyl compound that undergoes a tandem one-pot transformation with amine, affording the corresponding amide[5]. In general, the reaction does not require an acid, a stoichiometric oxidant, or additives, and generates hydrogen gas as the only by-product.

1.3.2 Conventional amide bond formation method

Amide bond formation is one of the most important reactions in organic chemistry[6]. Although most pharmaceutical and bioactive compounds contain amide bonds, the existing synthetic methods for the formation of amide bonds suffer from hazardous nature, high cost, and poor synthetic economy. Amides are highly polar and stable as shown in Scheme 1.4. Various conformations are possible for amides in polypeptides, proteins, and other synthetic polymers. In living systems, the key reaction in protein synthesis by ribosomes is the transformation of activated esters to the corresponding amides[7] . In laboratory synthesis, amides are synthesized by the coupling reactions of activated carboxylic acids or acyl halides with amines using strong coupling reagents [6b,6c]. During this process, toxic halide wastes and large amounts of

unreacted chemicals are generated. Because amide bonds are still widely used, development of sustainable synthetic methods is a top challenge in organic chemistry[8].

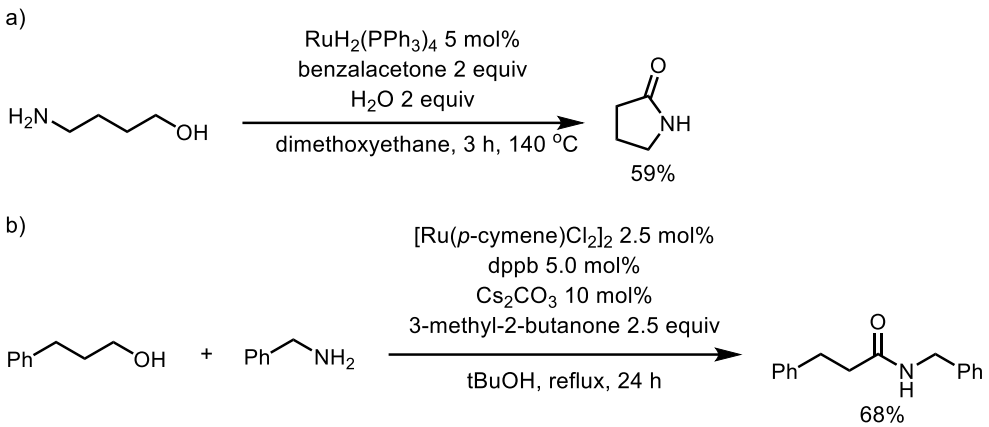


Scheme 1.4 a) Chemical structures of amides and b) conventional amide synthetic methods

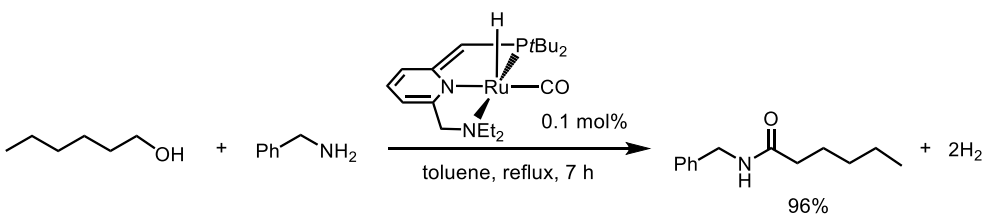
1.3.3 Metal-catalyzed dehydrogenative synthesis of amide

The first dehydrogenative amide synthesis was reported by Murahashi in 1971 using $[RuH_2(PPh_3)_4]$ in the presence of a hydrogen acceptor (Scheme 1.5a)[9]. Five and six-membered lactams were prepared from amino alcohols via intramolecular dehydrogenative amidation. Williams also reported intermolecular amide bond formation using $[Ru(p\text{-cymene})Cl_2]_2$, a phosphine

ligand system, and a hydrogen acceptor (Scheme 1.5b)[10].



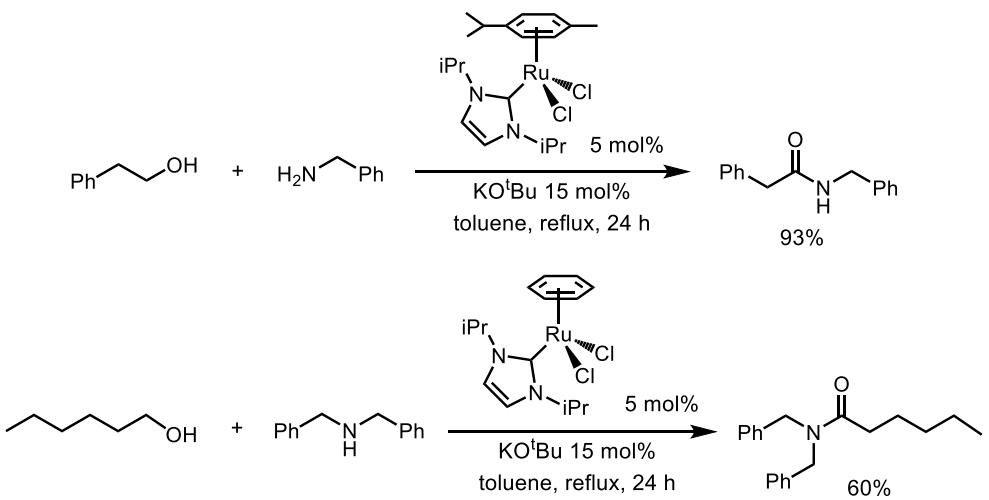
Scheme 1.5 a) The first dehydrogenative amide synthesis by Murahashi and b) Williams group



Scheme 1.6 Ruthenium PNN-pincer-catalyzed dehydrogenative amide synthesis by Milstein

An important breakthrough was the development of a Ru pincer complex reported by Milstein (Scheme 1.6)[5a]. Without using a base or hydrogen acceptor, various amides were obtained based on the catalyst performance via alternative aromatizing and dearomatizing processes during the catalytic cycle, facilitating the

dehydrogenation of alcohol. In the expansion of this study, our research group also developed a separate catalytic system using a Ru–NHC complex and a strong base[11]. When the *p*–cymene ring of the catalyst was replaced with benzene, a superior activity was observed for secondary amines and sterically hindered amines (Scheme 1.7)[12]. A series of *in situ* generated catalysts were also developed. A catalytic system comprising [$RuH_2(PPh_3)_4$], NHC precursor, NaH, and CH_3CN showed excellent performance in the synthesis of amides from both alcohols and aldehydes (Figure 1.1)[12–13].



Scheme 1.7 Ru–NHC system developed by Hong

In the mechanism, a carbonyl group is formed by metal–prompted dehydrogenation of alcohol, which is coupled with amine to give a

hemiaminal intermediate. This undergoes further dehydrogenation to form an amide (Scheme 1.8).

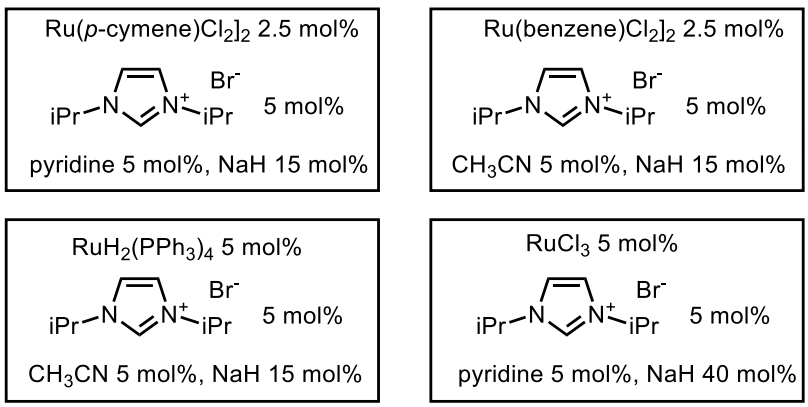
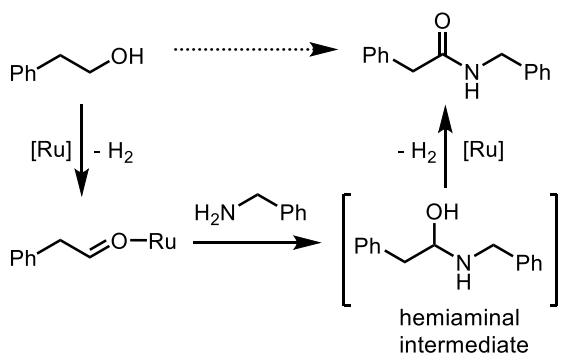


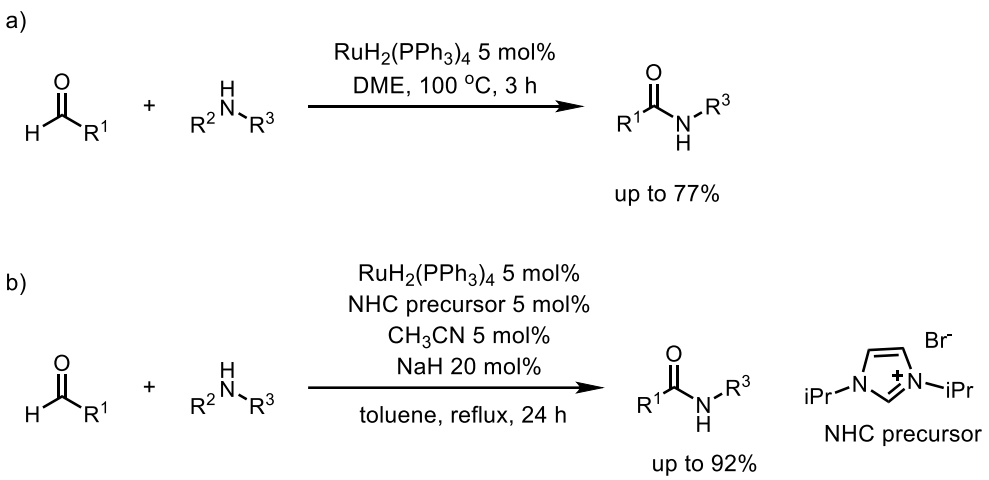
Figure 1.1 *In situ* generated system by Hong



Scheme 1.8 Mechanism of dehydrogenative amide synthesis

1.3.4 Other dehydrogenative amide synthesis methods

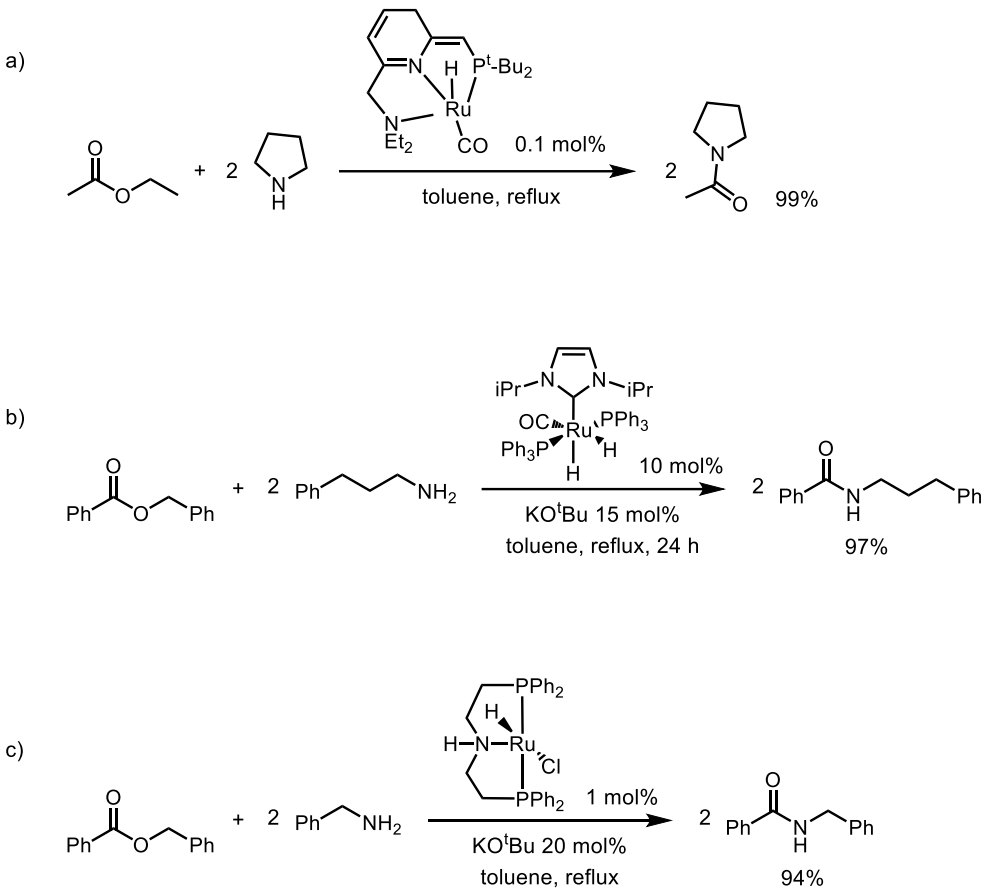
Ru-catalyzed amide formation from an aldehyde and amine is also an attractive approach with a high atom economy because only a hydrogen molecule is generated as the by-product [9].



Scheme 1.9 Dehydrogenative amidation of aldehydes with amines

In 1991, Murahashi group disclosed dehydrogenative amide synthesis from an aldehyde and amine (Scheme 1.9a)[9]. The substrate scopes were limited to aromatic aldehydes and cyclic secondary amines. More improved system was reported by the Hong group in 2010 with a broader substrate scope including the use of primary amines as the starting materials (scheme 1.9b)[12]. Generally, aldehyde reacts with an amine to produce hemiaminal intermediate which is oxidized to the corresponding amide with the

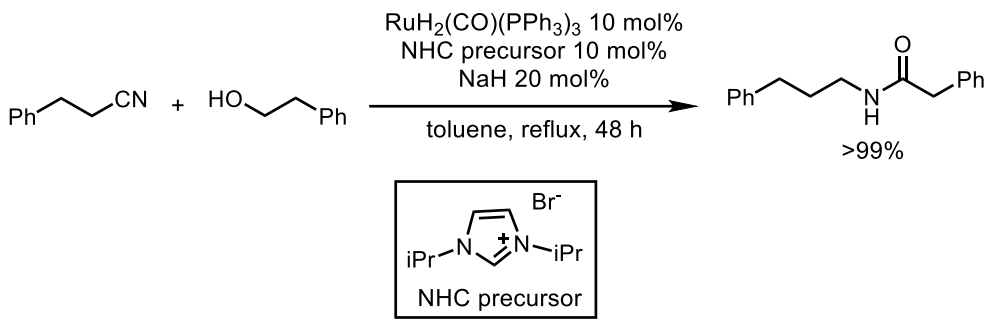
help of ruthenium catalyst.



Scheme 1.10 Dehydrogenative amidation from esters and amines

Ester amidation is another important method to form amide bonds with a key protein synthesis mechanism *in vivo*[7c]. Milstein and coworkers first disclosed this transformation using a pincer Ru catalyst obtained from symmetrical esters [14](Scheme 1.10a) Unactivated aliphatic esters were successfully converted to 2 equiv

of the corresponding amides per ester. The Hong group found that the combination of a NHC–Ru complex with a strong base was active for the formation of amides from esters (Scheme 1.10b)[14b]. The Xiong also reported ester amidation using commercially available Ru–MACHO complex [15] (Scheme 1.10c).



Scheme 1.11 [Ru]–catalyzed redox–neutral amidation of nitriles with alcohols

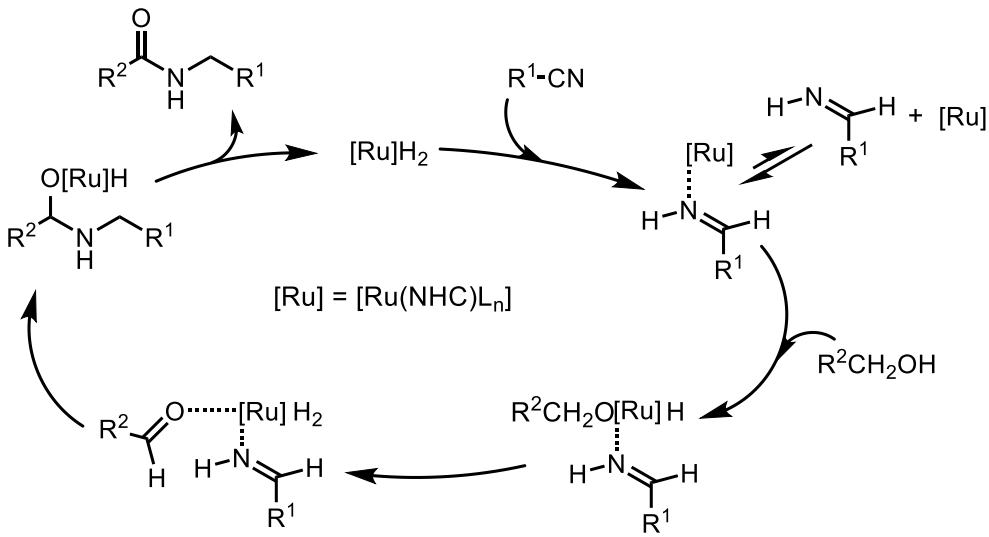


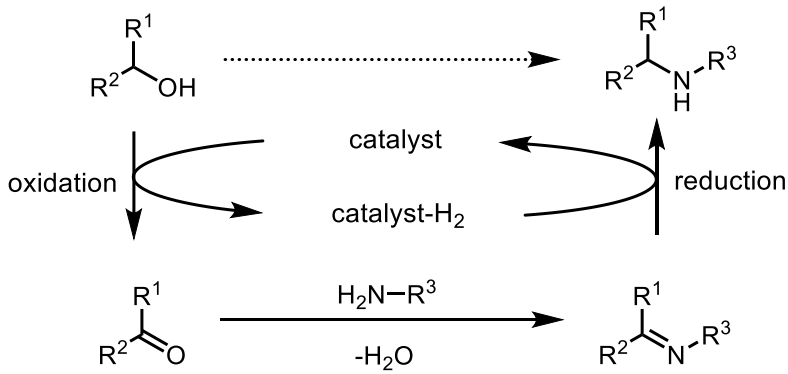
Figure 1.2 Mechanism of Ru-catalyzed amidation of nitrile

In 2013, Hong developed a highly efficient amide formation strategy using a nitrile as the amine surrogate (Scheme 1.11)[16]. It is completely redox-neutral in which oxidation of alcohol is coupled with reduction of nitrile. This reaction is completely redox-neutral in which the oxidation of an alcohol is coupled with the reduction of a nitrile. They found that a Ru bound aldehyde species is generated during the reaction by NMR study.

1.4 Borrowing hydrogen method

1.4.1 Introduction

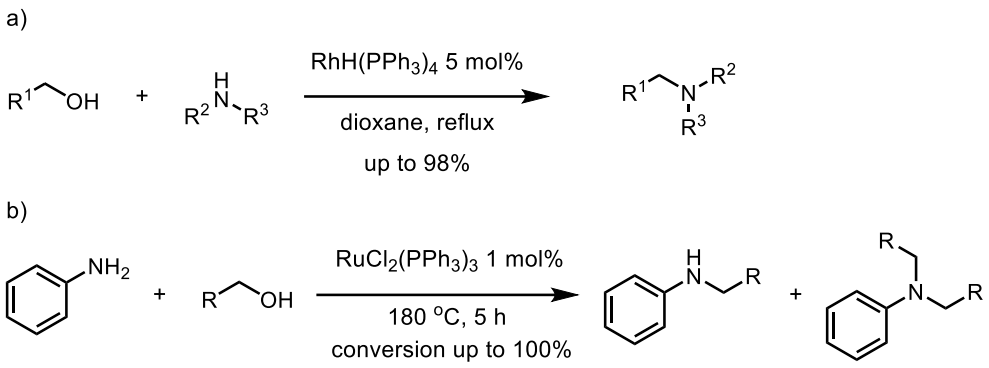
In dehydrogenative amide synthesis, the hydrogen gas generated from the substrate is removed or transferred to a hydrogen acceptor, and it is a net oxidative functionalization method. In fact, a closely related strategy known as "borrowing-hydrogen method" has a much longer history in the field of metal-catalyzed alcohol activation. Combining transfer hydrogenation with *in situ* functionalization, numerous methodological variations are possible as a sustainable alternative to conventional alkylation reactions (Scheme 1.12). This is known as the "borrowing-hydrogen" method where the alcohol is activated to a carbonyl compound by temporary hydrogen abstraction *in situ*. Condensation with nucleophile immediately reduces the carbonyl compound to the corresponding saturated product. Overall, a new C-N bond is formed in one step when an amine is used as the nucleophile. This reaction is net redox-neutral, and hydrogen gas not evolved. Water is eliminated as the only by-product.



Scheme 1.12 Borrowing hydrogen method

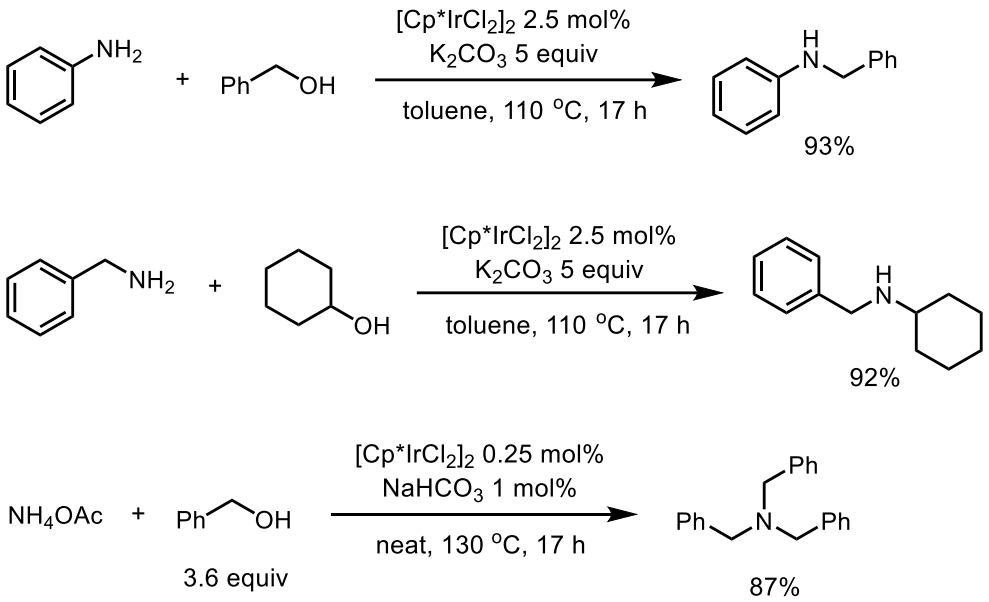
1.4.2 Transition metal catalyzed *N*-alkylation of amines with alcohols

In 1981, Grigg et al[17]. and Watanabe et al[18]. reported the first N-alkylation of amines with alcohols using a homogeneous catalyst (Scheme 1.13). Watanabe group reported the first example using the ruthenium catalyzed *N*-alkylation of anilines using both alcohols and aldehydes. Since the first development of N-alkylation of amines with alcohols, extensive progress has been made, mostly using ruthenium and iridium-based catalysts.



Scheme 1.13 The first example of *N*-alkylation of amines with alcohols by a) Grigg and b) Watanabe

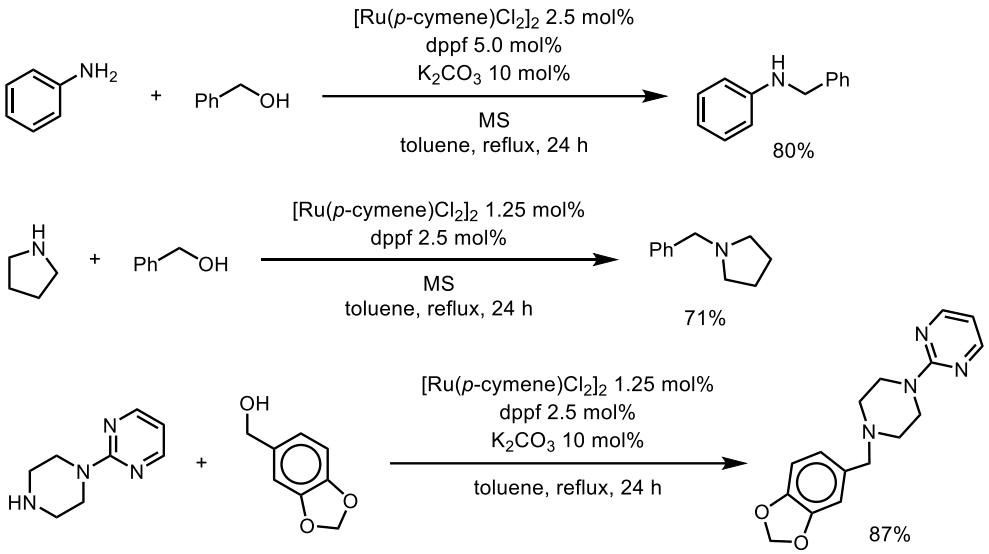
Fujita and Yamaguchi group pioneered this reaction by utilizing commercially available $[Cp^*IrCl_2]_2$ and K_2CO_3 as an effective catalytic system for the alkylation of anilines with benzyl alcohol in quantitative conversion (Scheme 1.14)[19]. Notably, the catalytic system was successfully applied to the alkylation of alkyl amines with primary and secondary alcohols[20] and multiple alkylation was also achieved with ammonium acetate using this catalytic system[21].



Scheme 1.14 *N*-alkylation of amine with $[Cp^*IrCl_2]_2$ developed by Fujita and Yamaguchi group

Other ruthenium catalysts including $RuCl_2(PPh_3)_3$[22], $RuCl_3 \cdot nH_2O3P(OBu)_3$[23], $CpRu(PPh_3)_2Cl$[24] and $[Ru(PPh_3)_2(MeCN)_3Cl][BPh_4]$[25] have also been developed for alcohol amination. In 2007, Williams group found that a combination of $[Ru(p\text{-cymene})Cl_2]_2$ with bidentate phosphine dppf is a highly effective catalytic system for the synthesis of secondary or tertiary amines (Scheme 1.15)[26]. Using this system, they successfully achieved the alkylation of aryl amines and cyclic aliphatic amines. Interestingly, a pharmaceutically important compound, dopamine agonist Piribedil, was synthesized

by the reaction of piperazine with piperonyl alcohol[27].



Scheme 1.15 I-alkylation of amine with $[Ru(p\text{-cymene})Cl_2]_2$ developed by Williams group

In expansion of the study, the borrowing hydrogen method has been applied to the synthesis of N-heterocycles. Indoles, indolines, quinolones, benzoxazoles, and benzimidazoles were efficiently prepared using suitable substrates.

According to the mechanism, both amide synthesis and *N*-alkylation proceed through a hemiaminal intermediate formed by the addition of an amine to an aldehyde. Irreversible release of

dihydrogen from the hemiaminal generates an amide. Instead, elimination of water followed by immediate reduction of the formed imine generates an amine as the product. Selectivity of the final product depends on the catalytic system, even though it is currently unclear what properties determine the selectivity. Huynh recently studied the selectivity of amide vs. amine formation by changing the base and solvent using the same Ru complex.

Dehydrogenative amide synthesis and *N*-alkylation via the borrowing-hydrogen method are consistent with the concept of green and sustainable chemistry. As described in this chapter, many chemists have dealt with the challenges existing in the synthesis of amides and amines. Considering the extensive use and future opportunities of these molecules in organic chemistry, pharmaceutical field, and biochemistry, however, there still remain much room for improvement such as access to highly functionalized amide-based structures, polymers, and biomimicking molecules.

1.5 Reference

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Chapter 2. Dehydrogenative Amide Synthesis: Azide as a Nitrogen Source*

2.1 Introduction

Atom-economical amide synthesis is one of the top challenges in synthetic organic chemistry. In 2005, members from the major pharmaceutical companies voted "amide bond formation avoiding poor atom economy reagents" as the highest challenge in green chemistry research area at the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable.[1] Amide bond is the key backbone of all natural peptides in biological systems and also favorable functional group in all branches of organic chemistry.[2] Traditionally, amide was synthesized by reactions of carboxylic acids and their derivatives with amines,[3] which suffers from harsh conditions and a large amount of byproduct. Over the past few years, chemists have extensively addressed new methodologies to amide linkage, aiming at more efficient and environmentally benign pathway.

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Interesting approaches include native chemical ligation[4] oxidative amidation of alcohols,[5,9] aldehydes,[6] or alkynes[7] and oxidative coupling of an R−bromonitroalkane[8] (Figure 2.1).

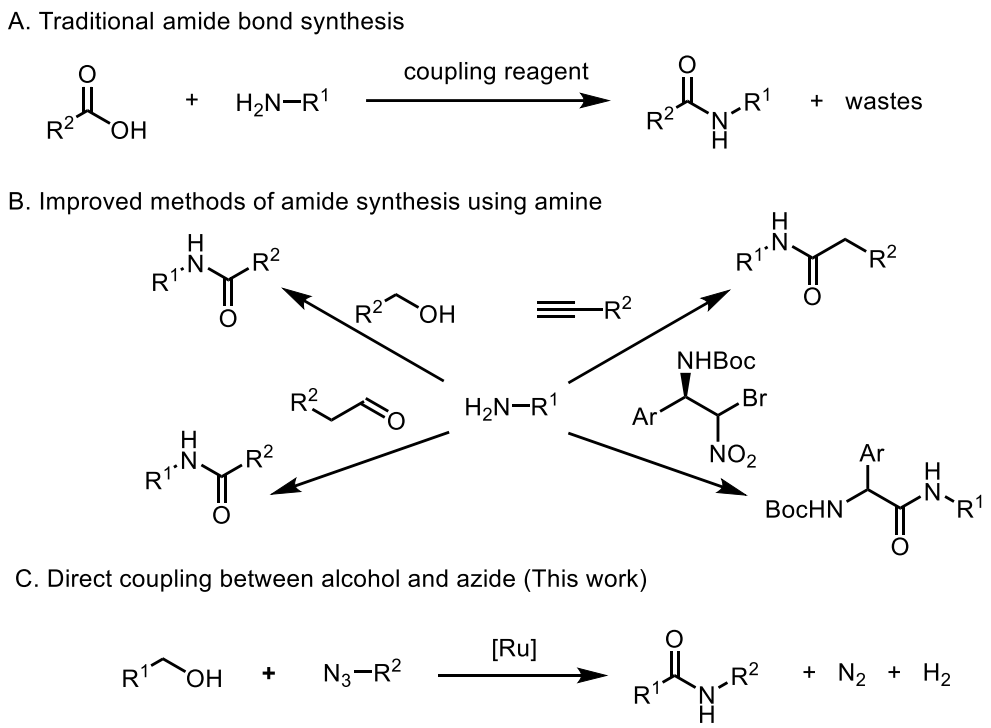


Figure 2.1 Different Strategies of Amide Synthesis

All these systems utilize amine, mostly primary amine, as an "N" atom source of amide. However, primary amine is one of the wayward reagents to organic chemists. Apart from the fact that one should endure its strong scent, it is tedious to purify and handle due to its

strong polarity. Therefore, accessibility to variety of primary amine substrates is limited. The use of primary amine surrogate would address these limitations for the amide synthesis.

Organic azides are one of the useful alternatives to primary amines.[9] Obviously, azides enjoy several advantages superior to primary amine: it is easily accessed from organic halides allowing a fruitful substrate variety, not toxic, has no trouble in isolation, and only liberating nitrogen gas as a reduction byproduct. Its high energy, dipolar structure allows versatile chemical transformations including cycloaddition,[10] nitrene chemistry,[11] Schmidt reaction[12] and others.[13]

During our studies on the atom-economical and environmentally benign amidation from an alcohol with an amine prompted by a ruthenium catalytic system,[14] we envisioned that amidation of alcohols could be achieved with azides in place of amines. Herein, we report an in situ generated catalyst based on $RuH_2(PPh_3)_4$ for the direct amide synthesis from azide and alcohol. To the best of our knowledge, this is the first example of a transition-metal based catalytic system that transforms an azide and alcohol directly into an amide in a single step.

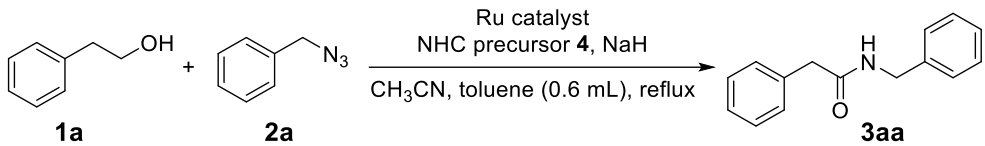
2.2 Result and discussion

2.2.1 Optimization for amide synthesis from azides and alcohols

The reaction of 2-phenylethanol (**1a**) and benzyl azide (**2a**) was chosen to investigate the catalytic conditions to realize the amidation of alcohol with azide (Table 2.1). A series of ruthenium complexes with the help of the N-heterocyclic carbene (NHC) ligand generated from 1,3-diisopropylimidazolium bromide (**4**) and NaH, well known catalysts for the oxidative amide synthesis from alcohols,[14] were selected as the pre-catalyst complexes. The role of NaH has been suggested to activate the precatalyst as well as to generate the NHC ligand from **4**.[14] The $[Ru(benzene)Cl_2]_2$-based catalyst did not exhibit any activity for the target reaction (Table 2.1, entry 1). A trace amount of amide was detected with catalytic systems using $[Ru(p\text{-cymene})Cl_2]_2$, $RuCl_3$, and Shvo's complex (Table 2.1, entries 2-4). Then we noticed that several ruthenium hydride complexes exhibited improved activities (Table 2.1, entries 5-7). Among them, $RuH_2(PPh_3)_4$ displayed the best activity for this transformation. The desired amide product **3aa** was obtained in 33% yield for 24 h (Table 2.1, entry 7). When the reaction time was prolonged to 48 h, the yield of amide **3aa** reached up to 73%(Table 2.1, entry 8). The reaction efficiency was sensitive to the ratio of azide and alcohol. We found

that the reaction with a slightly higher amount of alcohol **1a** than that of **2a** (**2a**:**1a**=1:1.2) provided the amide product **3aa** in quantitative GC yield and 92% isolated yield (Table 2.1, entry 12).

Table 2.1 Catalyst Screening[a]



Entry	**2a/1a**	[Ru]	Time (h)	Yield (%)[b]
1	1.1	$[Ru(benzene)Cl_2]_2$	24	0
2	1.1	$[Ru(p\text{-cymene})Cl_2]_2$	24	<5
3	1.1	$RuCl_3$	24	<5
4	1.1	Shvo's complex[c]	24	<5
5	1.1	$RuH_2(CO)(PPh_3)_3$	24	23
6	1.1	$RuHCl(CO)(PPh_3)_3$	24	29
7	1.1	$RuH_2(PPh_3)_4$	24	33
8	1.1	$RuH_2(PPh_3)_4$	48	73
9	1.5	$RuH_2(PPh_3)_4$	48	78
10	2.0	$RuH_2(PPh_3)_4$	48	84
11	1:1.1	$RuH_2(PPh_3)_4$	48	76

12	1:1.2	$RuH_2(PPh_3)_4$	48	100

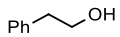
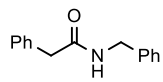
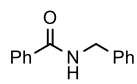
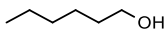
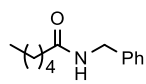
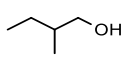
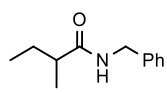
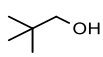
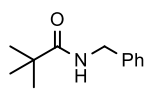
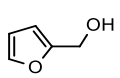
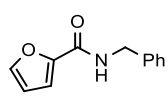
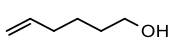
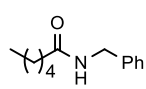
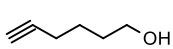
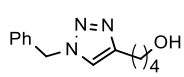
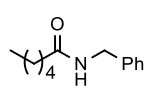
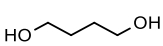
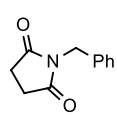
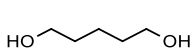
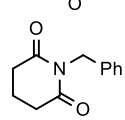
[a] Reaction conditions: **2a** (0.5mmol scale), **1a**, Ru complex (5 mol%), **4** (5 mol%), NaH (20 mol%), CH_3CN (5 mol%), toluene (0.6 mL), reflux, 48 h. [b] Yields were determined by GC using dodecane as an internal standard. [c] Shvo's complex = (1-hydroxytetraphenyl cyclopentadienyl-(tetraphenyl-2,4-cyclopentadien-1-one)-μ-hydrotetracarbonyl diruthenium(II)

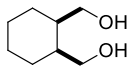
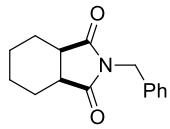
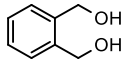
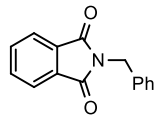
2.2.2 Substrate scope

With the optimized conditions in hand, we examined the generality of this protocol. First, the feasibility of this method was evaluated by the reaction of benzyl azide with a range of alcohols (Table 2.2). Benzyl alcohol generated the corresponding amide with an excellent yield of 94%, and aliphatic alcohols also showed excellent activity (entries 1-3). Sterically hindered alcohols led to formation of the correspondingamides with lowered yields (entries 4 and 5). 2-Furanmethanol (**1f**) also provided the amide **3fa** in 80% yield (entry 6). When using 5-hexen-1-ol as a starting material, the reduction of the unsaturated double bond in the alcohol occurred with the formation of the corresponding amide in 73% yield (entry 7).

One of the most significant uses of azide is in the [3 + 2] cycloaddition reaction with alkyne.[15]

Table 2.2 Synthesis of Amide and Imides from Benzyl Azide **2a** and Alcohols[a]

Entry	Alcohol		Product[b]		Yield (%)[b]
1		**1a**		**3aa**	92
2		**1b**		**3ba**	94
3		**1c**		**3ca**	90
4		**1d**		**3da**	76
5		**1e**		**3ea**	49[c]
6		**1f**		**3fa**	80
7		**1g**		**3ca**	73
8		**1h**		**3ha**	35
				**3ca**	27
9		**1i**		**3ia**	75
10		**1j**		**3ja**	40

11		1k		3ka	67[d]
12		1l		3la	52[d]

[a]Reaction conditions: **2a** (0.5 mmol, 1.0 equiv), alcohol (1.2 equiv), $RuH_2(PPh_3)_4$ (5 mol%), **4** (5 mol %), NaH (20 mol %), CH_3CN (5 mol %), toluene (0.6 mL), reflux, 48 h. [b]Yields are of the isolated product, and represent the average of at least two runs. [c]NaH (40 mol %), toluene (0.3 mL). [d]toluene (0.3 mL).

To investigate the chemoselectivity of our catalytic system, we chose the reaction with an alcohol possessing an alkyne functional group. When 5-hexyn-1-ol and benzyl azide were employed, the corresponding amide **3ca** was obtained in 27% yield along with 1,4-disubstituted 1,2,3-triazole compound **3ha** (entry 8).[16]

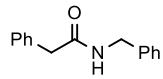
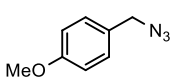
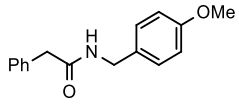
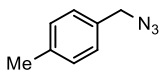
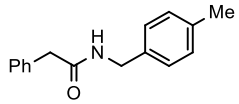
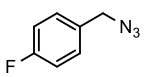
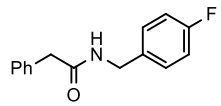
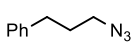
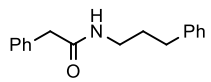
Next, another noticeable result was obtained, based on our recent work including efficient synthesis of cyclic imides from amines and diols under the same catalytic system.[17] Various cyclic imides were synthesized from benzyl azide and diols in 40% to 75% yields (entries 9-12). Syntheses of five-membered succinimides (entries 9 and 11), a six-membered glutarimide (entry 10), and a phthalimide derivative (entry 12) were demonstrated.

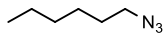
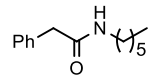
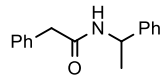
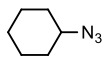
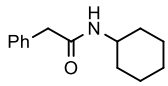
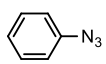
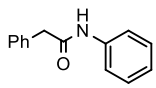
The scope of azide components was expanded using 2-

phenylethanol (Table 2.3). Both electron-donating and -withdrawing substituents on the aromatic ring furnished the corresponding amides with good to excellent yields (entries 2-4).

The electron-withdrawing fluoro group led to a reduced yield of **3ad** (entry 4). Sterically hindered azides also generated the corresponding amides in moderate yields (entries 7 and 8). Aromatic azides such as phenyl azide gave the amide in a significantly low yield of 22% (entry 9). Sensitivity to sterics and *N*-nucleophilicity have been also well reported in the direct amidation from alcohols and amines.[5,14]

Table 2.3 Synthesis of Amide from 2-Phenylethanol **1a** and Azides[a]

Entry	Azide		Product		Yield (%)[b]
1		**2a**		**3aa**	92
2		**2b**		**3ab**	94
3		**2c**		**3ac**	90
4		**2d**		**3ad**	77
5		**2e**		**3ae**	90

6		2f		3af	92
7		2g		3ag	54[c]
8		2h		3ah	61
9		2i		3ai	22[d]

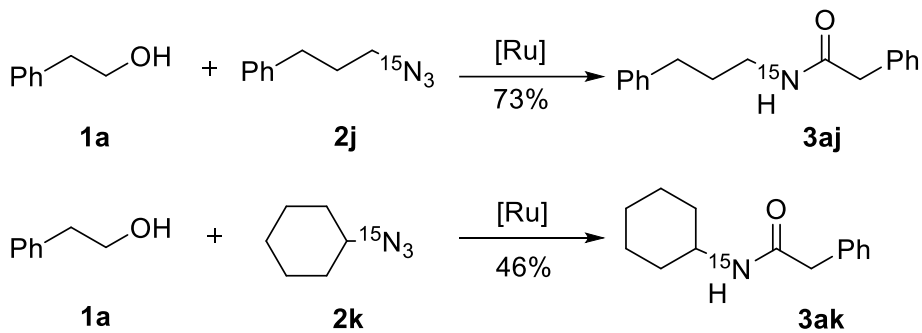
[a]Reaction conditions: Azide (0.5 mmol, 1.0 equiv), **1a** (1.2 equiv), $RuH_2(PPh_3)_4$ (5 mol%), **4** (5 mol %), NaH (20 mol %), CH_3CN (5 mol %), toluene (0.6 mL), reflux, 48 h. [b]Yields are of the isolated product, and represent the average of at least two runs. [c]NaH (40 mol %), toluene (0.3 mL). [d]mesitylene(0.6 mL) at reflux.

2.2.3 Isotope labeled amide syntheis

Considering the importance of isotope labeled peptides and proteins in medical and biological studies,[18] we explored the utility of the reaction by performing an ^{15}N-isotope labeling experiment. The reaction of 2-phenylethanol and ^{15}N-labeled 3-phenylpropylazide under the optimized conditions gave the desired amide **3aj** in 73% yield. ^{15}N-labeled cyclohexylazide also gave the corresponding amide **3ak** in 46% yield (Scheme 2.1). As easily manageable ^{15}N-labeled azides are readily accessible in one step from alkyl halides and commercially available ^{15}N-labeled NaN_3, facile access to ^{15}N-

labeled amides bearing various functional groups could be realized with this methodology.

Scheme 2.1 Isotope Labelling Study



Azide (0.5 mmol, 1.0 equiv), **1a** (1.2 equiv), $RuH_2(PPh_3)_4$ (5 mol%), **4** (5 mol %), NaH (20 mol %), CH_3CN (5 mol %), toluene (0.6 mL), reflux, 48 h. Yields are of isolated products. >40% ^{15}N incorporation based on NMR analysis (see the Supporting Information).

2.2.4 Mechanism study

Next, we investigated the mechanism of this direct amidation from azide and alcohol. Initially, we suspected the involvement of aza-ylide for the transformation. It has been well reported that organoazide ligates carboxylic acid or ester to give amide in the

presence of triphenylphosphine.[19] Therefore, we applied the same reaction condition on (benzylimino)triphenylphosphorane **4a**, which is independently prepared by the Staudinger reaction of benzyl azide and triphenylphosphine, with 2-phenylethanol. However, no reaction occurred. This result excluded the possibility of aza-ylide involvement in the reaction.

Kinetic studies, performed by monitoring the reaction progress between 2-phenylethanol (**1a**) and *p*-methoxybenzyl azide (**2b**), gave a conclusive idea on the mechanism (Figure 2.2). At the very initial stage of the reaction, *p*-methoxybenzyl amine (**5b**) was detected along with the rapid consumption of **2b**. The concentration of **5b** was slowly decreased while that of amide **3ab** increasing. These results strongly led us to have the reaction mechanism shown in Scheme 2.3. First, azide was mainly reduced to amine by hydrogen transferred from alcohol dehydrogenation.

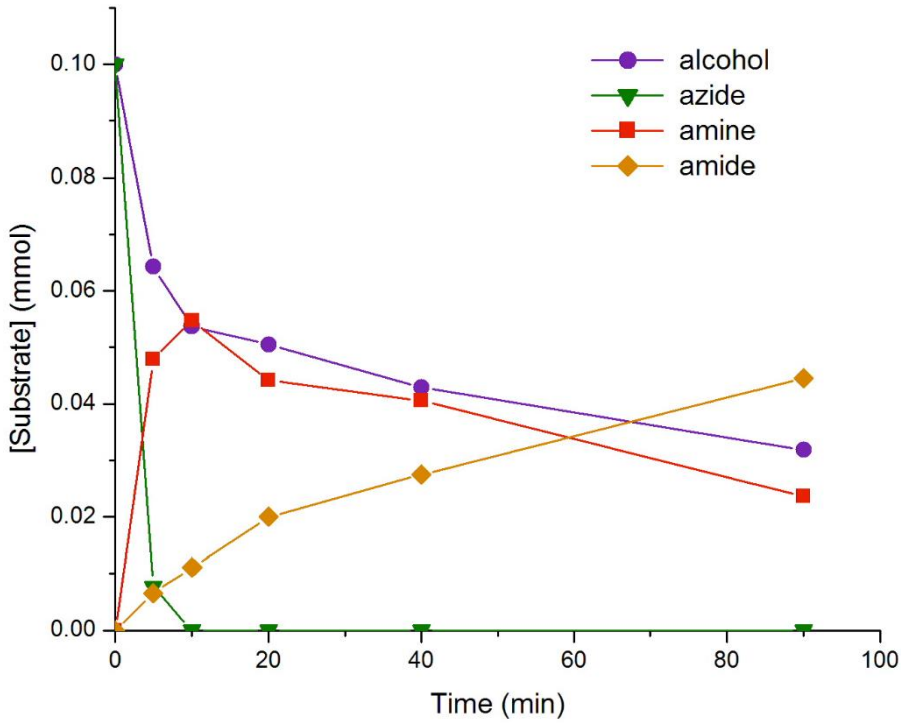
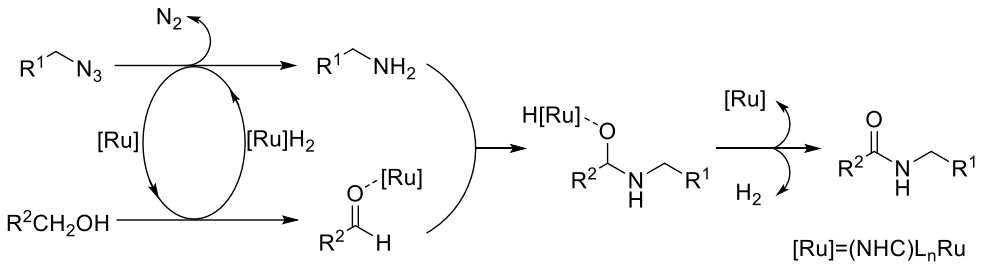


Figure 2.2 Reaction profiles showing the amount changes of substrate and product. Azide (**2b**, 0.10 mmol, 1.0 equiv), alcohol (**1a**, 1.0 equiv), $RuH_2(PPh_3)_4$ (5 mol %), **4** (5 mol %), NaH (20 mol%), CH_3CN (5 mol %), toluene (0.12 mL), reflux. Data represent the average of three runs. The reaction progress was monitored by GC.

Next steps followed the same reaction mechanism suggested in the oxidative amide synthesis from alcohol and amine.[1] The generated aldehyde intermediate was subsequently attacked by the amine to form the hemiaminal intermediate. Finally, further dehydrogenation of the hemiaminal gave the amide product.

Scheme 2.3. Proposed Mechanism of Amide Synthesis Directly from Azide and Alcohol



2.3 Conclusion

We have demonstrated for the first time that direct amide synthesis from azide and alcohol is possible. This fundamental but important transformation allows atom economical and direct synthesis of amide bond producing hydrogen and nitrogen gas as the sole by-products. The reaction has a broad substrate generality including diols for the synthesis of cyclic imides. In addition, ^{15}N-labelled amide could be prepared in one step using readily available ^{15}N-labelled azide and alcohol. This expansion of N-source for the atom-economical amide syntheses will make one step forward to achieve environmentally benign amide synthesis.

2.4 Experimental section

2.4.1 General information

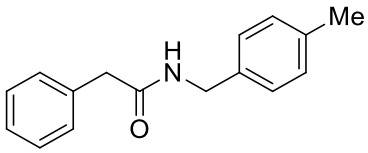
Unless otherwise noted, all reactions were carried out using standard Schlenk techniques or in an argon-filled glove box. Dichloromethane, diethyl ether and toluene were dried over Pure Solv solvent purification system. NMR spectra were recorded in $CDCl_3$, CD_2Cl_2 or toluene-d_8 using Bruker DPX300, AMX400, JEOL ECA400 or JEOL ECA400SL spectrometer, and TMS (tetramethylsilane) was used as a reference. Chemical shifts were reported in ppm and coupling constant in Hz. GC analyses were carried out with 7080A GC system from Agilent Technologies, equipped with an HP-5 column. $RuH_2(PPh_3)_4$,[1] $RuH_2(CO)(PPh_3)_3$,[2] $RuHCl(CO)(PPh_3)_3$,[2] 1,3-diisopropylimdazolium bromide (**4**)[3] and all of azides[4] were prepared by literature procedures. ^{15}N isotope labeled sodium azide was purchased from Cambridge Isotope Laboratories, Inc. (1-^{15}N, 98%+). Other chemicals were purchased from commercial suppliers and used as received without further purification.

2.4.2 General procedure for amide synthesis

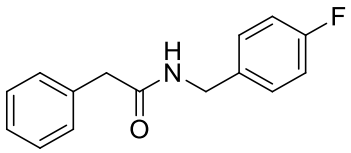
$RuH_2(PPh_3)_4$ (28 mg, 0.025 mmol), 1,3-diisopropylimidazolium bromide (5.8 mg, 0.025 mmol), NaH (2.4 mg, 0.10 mmol) and acetonitrile (1.2 μL, 0.025 mmol) were placed in an oven dried Schlenk tube inside the glove box; toluene (0.6 mL) was added to the mixture over there. The Schlenk tube was taken out and heated to reflux in an oil bath under an argon atmosphere. The flask was removed from the oil bath after 20 min and the alcohol (0.60 mmol) and azide (0.50 mmol) were added. The mixture was heated to reflux under argon for 48 h before being cooled to room temperature. All the volatiles were removed under vacuum. Purification of the crude product was performed by flash chromatography.

2.4.3 Characterization of Amides 3aa – 3ai.

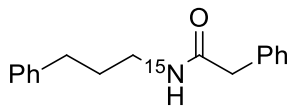
All reported compounds, **3aa**,[2] **3ba**,[2] **3ca**,[2] **3da**,[3] **3ea**,[2] **3fa**,[3] **3ha**,[4] **3ia**,[5] **3ja**,[5] **3ka**,[6] **3la**,[7] **3ab**,[8] **3ae**,[9] **3af**,[3] **3ag**,[10] **3ah**,[9] **3ai**,[1e] were identified by spectral comparison with literature data or with analogous literature data.



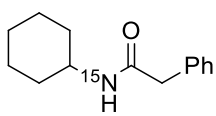
N-(4-Methylbenzyl)-2-phenylacetamide (3ac): white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.31 (s, 3H), 3.62 (s, 2H), 4.37 (d, J = 6.0 Hz, 2H), 5.63 (bs, 1H), 7.08 (dd, J = 17.2, 8.0 Hz, 4H), 7.26–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 170.8, 137.2, 135.1, 134.8, 129.5, 129.3, 129.0, 127.5, 127.4, 43.7, 43.4, 21.1; HRMS (ESI) calcd for $C_{16}H_{18}NO$: 240.1388 Found: 240.1386 [MH^+].



N-(4-Fluorobenzyl)-2-phenylacetamide (3ad): white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.61 (s, 2H), 4.35 (d, J = 6.0 Hz, 2H), 5.79 (bs, 1H), 6.94–6.98 (m, 2H), 7.14 (dd, J = 8.8, 5.6 Hz, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 170.9, 163.3, 160.9, 134.8, 134.0, 133.9, 129.4, 129.2, 129.1, 129.0, 127.5, 115.6, 115.4, 43.8, 41.9; HRMS (ESI) calcd for $C_{15}H_{15}FNO$: 244.1138 Found: 244.1141 [MH^+].



^{15}N-(3-Phenylpropyl)-2-phenylacetamide (3aj): white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.37–7.32 (m, 2H), 7.32–7.25 (m, 1H), 7.24–7.20 (m, 4H), 7.15 (t, J = 7.4 Hz, 1H), 7.10–7.04 (m, 2H), 5.30 (bs, 1H), 3.53 (s, 2H), 3.21 (dd, J = 13.2, 7.0 Hz, 2H) 2.58–2.49 (m, 2H), 1.74 (dt, J = 14.7, 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ = 171.2, 141.5, 135.2, 129.6, 129.2, 128.6, 128.5, 127.5, 126.2, 44.0, 39.4, 33.3, 31.2; 53% of ^{15}N incorporated (incorporation was determined by NMR integration value); HRMS (EI) calcd for $C_{17}H_{19}{}^{15}NO$: 254.1441 Found: 254.1441 [M^+].



^{15}N-Cyclohexyl-2-phenylacetamide (3ak): white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.36 (t, J = 7.3 Hz, 2H), 7.33–7.27 (m, 1H), 7.27–7.23 (m, 2H), 5.22 (bs, 1H), 3.80–3.70 (m, 1H), 3.54 (s, 2H), 1.85–1.80 (m, 2H), 1.68–1.52 (m, 3H), 1.39–1.25 (m, 2H), 1.14–0.94 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ = 170.1, 169.9, 169.8, 135.1, 129.4, 128.9, 127.2, 48.1, 44.0, 32.9, 25.4, 24.7; 52% of ^{15}N

incorporated (incorporation was determined by NMR integration value); HRMS (EI) calcd for $C_{14}H_{19}{}^{15}NO$: 218.1436 Found: 218.1436 [M^+].

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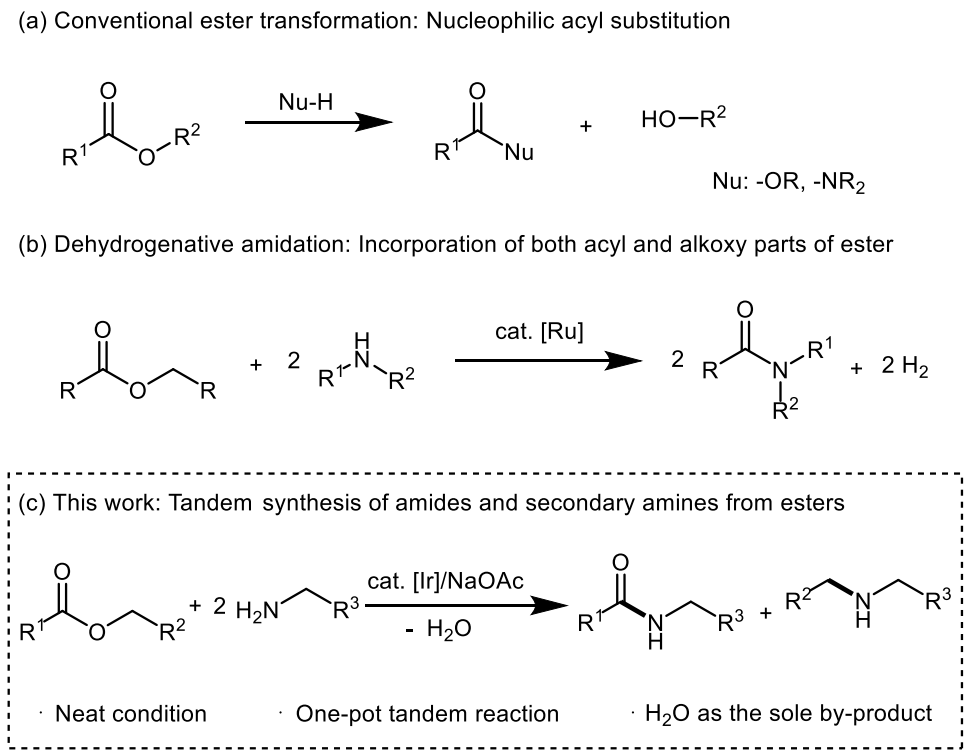
Chapter 3. Tandem Synthesis of Amides and Secondary Amines from Esters with Primary Amines under Solvent-Free Conditions*

3.1 Introduction

Esters are one of the most common functional groups in nature and constitute an important class of carboxylic acid derivatives. [1] They are present in animal fats and are responsible for the pleasant aroma of vegetable oils. In biological systems, peptide bonds are formed by the enzymatic conversion of esters catalyzed by ribosomes. Many classical routes and catalytic transformations of esters, including ester hydrolysis, transesterification, and ester reduction to alcohol/aldehyde, are well documented.[1-2] In addition, the ester-amide exchange reaction is an important process and catalytic methods have also been reported. [3]

* The majority of this work has been published: Jeongbin Lee, Senthilkumar Muthaiah, and Soon Hyeok Hong*, *Adv. Synth. Catal.* 2014, *356*, 2653 - 2660.



Scheme 3.1 Different ester transformation methods

Recently, the Mashima group demonstrated that a catalytic amount of sodium methoxide is capable of converting various esters into amides under mild conditions.[3a] The development of catalytic protocols for such reactions has been oriented toward the efficient nucleophilic acyl substitutions of esters, with subsequent liberation of the corresponding alcohol (Scheme 3.1a). Thus methyl or ethyl esters have been commonly used to produce methanol or ethanol respectively as the corresponding alcohol.

One-pot multiple functionalization facilitates more than two transformations forming several bonds with less waste and greater economic benefits.[4] Although numerous synthetic transformations of esters have been reported, few attempts have been made to utilize the generated alcohols from esters in one-pot reactions. Such a reaction would be attractive as the synthetic versatility of ester transformations could be enhanced. The seminal work by the Milstein group in the synthesis of amides from esters demonstrated that both the acyl and alkoxy parts of the ester starting material participated in the reaction by sequential ruthenium catalyzed transformations (Scheme 3.1b).

The transition metal-catalyzed alkylation of amines with alcohols is one of the most promising methods for the synthesis of secondary amines.[5] The reaction proceeds by "borrowing hydrogen", also known as the hydrogen auto-transfer method. The mechanism involves the dehydrogenation of the alcohol to the corresponding carbonyl compound followed by the formation of imine and its reduction to amine by the metal-hydride complex formed in the first step.

We focused on the fact that esters can provide alcohols that can be used as an amine alkylation source. Hence we planned to develop a

novel C–N bond formation method involving the following: 1) the formation of amide bonds by the nucleophilic acyl substitution of esters with amines and 2) the synthesis of secondary amines by the reaction of the in situ generated alcohols with primary amines by the borrowing hydrogen method. To the best of our knowledge, this is the first report that documents the utilization of esters as the direct carbon sources for amides and amines in one-pot sequential reactions.

3.2 Result and discussion

3.2.1 Optimization of the reaction

In order to realize our plan, the reaction of benzyl acetate **1a** with phenethylamine **2a** was chosen as the model reaction. Based on the reported systems for the alkylation of amines with alcohols, we evaluated a series of iridium[6] and ruthenium[7] catalytic systems (Table 3.1). Initially the catalytic system consisting of $[Ru(p\text{-cymene})Cl_2]_2$, a phosphine ligand (dppf) and K_2CO_3[7c] afforded only a trace amount of **4aa** (Table 3.1, entry 1). However, changing the catalyst system to $[Cp^*IrCl_2]_2$ and K_2CO_3[6e] resulted in improved yields (Table 3.1, entry 7). Therefore, we investigated several other

bases in combination with $[Cp^*IrCl_2]_2$ at different catalyst loadings (Table 3.1, entries 7–18).

Table 3.1 Optimization of reaction condition

Entry[a]	Catalyst (mol%)	Base (mol%)	Yield of **3aa**[c]	Yield of **4aa**[c]
1 (A)	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5)/dppf[c] (5 mol%)	K_2CO_3 (10)	64%	4%
2 (B)	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5)/dppf[c] (5 mol%)	K_2CO_3 (10)	50%	24%
3 (B)	$[Ru(benzene)Cl_2]_2$ (2.5)/dppf[c] (5 mol%)	K_2CO_3 (10)	60%	26%
4 (B)	$[(COD)IrCl]_2$ (2.5)	K_2CO_3 (10)	41%	9%
5 (B)	$Ir(CO)Cl(PPh_3)_2$ (2.5)	K_2CO_3 (10)	98%	16%
6 (B)	$IrH(CO)(PPh_3)_3$ (2.5)	K_2CO_3 (10)	63%	27%
7 (B)	$[Cp^*IrCl_2]_2$ (2.5)	K_2CO_3 (10)	60%	31%
8 (A)	$[Cp^*IrCl_2]_2$ (2.5)	K_2CO_3 (10)	80%	44%
9 (A)	$[Cp^*IrCl_2]_2$ (2.5)	K_2CO_3 (5)	81%	38%
10 (A)	$[Cp^*IrCl_2]_2$ (2.5)	Na_2CO_3 (5)	62%	46%
11 (A)	$[Cp^*IrCl_2]_2$ (2.5)	$NaHCO_3$ (5)	69%	57%
12 (A)	$[Cp^*IrCl_2]_2$ (2.5)	Cs_2CO_3 (5)	63%	52%
13 (A)	$[Cp^*IrCl_2]_2$ (2.5)	NaOMe (5)	90%	73%
14 (A)	$[Cp^*IrCl_2]_2$ (2.5)	NaOMe (2)	73%	48%
15 (A)	$[Cp^*IrCl_2]_2$ (2.5)	NaOAc (5)	93%	66%
16 (A)	$[Cp^*IrCl_2]_2$ (2.5)	NaOAc (2.5)	99%	71%
17 (C)	$[Cp^*IrCl_2]_2$ (1.25)	NaOAc (2.5)	>99%	73%
18 (D)	**$[Cp^*IrCl_2]_2$ (1.25)**	**NaOAc (2.5)**	**>99%**	**77%**

[a] Reaction conditions: (A) solvent, toluene (0.8 M); reaction temperature,

115 °C; reaction time, 36 h; (B) solvent, xylene (0.8M); reaction temperature, 145 °C; reaction time, 36 h; (C) neat; reaction temperature, 115 °C; reaction time, 36 h; (D) neat; reaction temperature, 115 °C; reaction time, 24 h. [b] GC yields using dodecane as the internal standard. [c] dppf=1,1'-bis(diphenylphosphino)ferrocene.

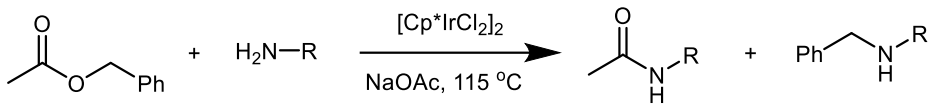
Compared to the carbonate bases, NaOMe showed better activity in toluene under reflux for 36 h. However, reducing the base loading, the yields decreased, particularly for **4aa** (Table 3.1, entries 13 and 14). Gratifyingly, the use of 2.5 mol% of NaOAc in toluene under reflux for 36 h afforded **3aa** and **4aa** in excellent and good yields respectively (Table 3.1, entry 16). The reduction of the catalyst loading to 1.25 mol% did not affect the yields of products (Table 3.1, entry 17). To our delight, the reactions run without solvent resulted in the highest yield at a reduced reaction time of 24 h (Table 3.1, entry 18).[8]

3.2.2 Substrate scope

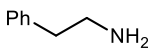
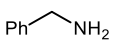
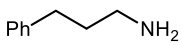
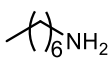
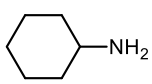
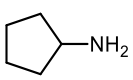
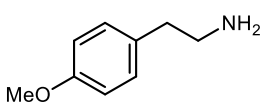
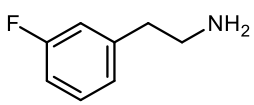
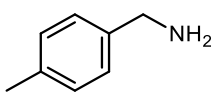
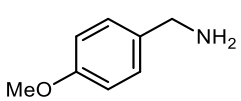
With the optimized reaction conditions in hand (Table 3.1, conditions D), amides and secondary amines were synthesized from diverse esters and primary amines. First, the reactions of 1a and various primary amines were explored (Table 3.2); the

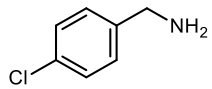
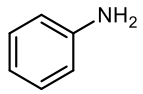
corresponding amides and secondary amines were obtained in good to high yields.

Table 3.2 Synthesis of amides and secondary amines from different amines and **1a**.



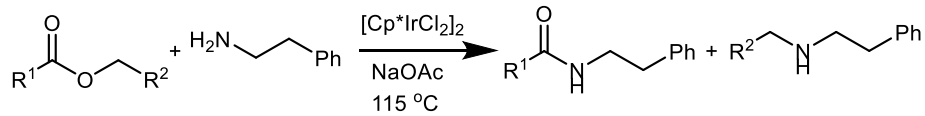
1a **2** (2.2 equiv) **3** **4**

Entry[a]	Amines		Yields of **3**[b] (%)	Yields of **4**[b] (%)
1		**2a**	**3aa** : 99	**4aa** : 69
2		**2b**	**3ab** : 98	**4ab** : 67
3		**2c**	**3ac** : 99	**4ac** : 66
4		**2d**	**3ad** : 86	**4ad** : 65
5		**2e**	**3ae** : 82	**4ae** : 60
6		**2f**	**3af** : 98	**4af** : 40
7		**2g**	**3ag** : 86	**4ag** : 75
8		**2h**	**3ah** : 99	**4ah** : 66
9		**2i**	**3ai** : 90	**4ai** : 70
10		**2j**	**3aj** : 98	**4aj** : 47

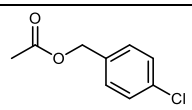
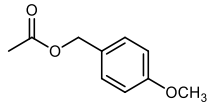
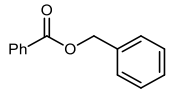
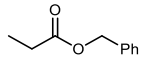
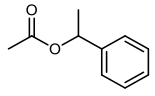
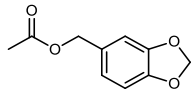
11		2k	3ak : 90	4ak: 67
12		2l	3al : 29	4al : 6

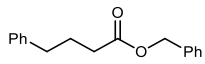
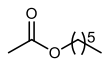
[a] Reaction conditions: 1a (0.5 mmol, 1.0 equiv.), 2 (2.2 equiv.), $[Cp^*IrCl_2]_2$ (1.25 mol%), NaOAc (2.5 mol%), 24 h. [b] Isolated yields.

Table 3.3 Synthesis of amides and secondary amines from different esters and 2a.



1 2a (2.2 equiv) 3 4

Entry[a)]	Esters		Yields of 3[b)] (%)	Yields of 4[b)] (%)
1		1b	98 3ba	69 4ba
2		1c	97 3ca	59 4ca
3		1d	68 3da	62 4da
4		1e	98 3ea	67 4ea
5		1f	82 3fa	30 4fa
6		1g	97 3ga	6 4ga

7		1h	73 3ha	69 4ha
8		1i	83 3ia	61 4ia

[a] Reaction conditions: 1 (0.5 mmol, 1.0 equiv.), 2a (2.2 equiv.), $[Cp^*IrCl_2]_2$ (1.25 mol%), NaOAc (2.5 mol%), 24 h. [b] Isolated yields.

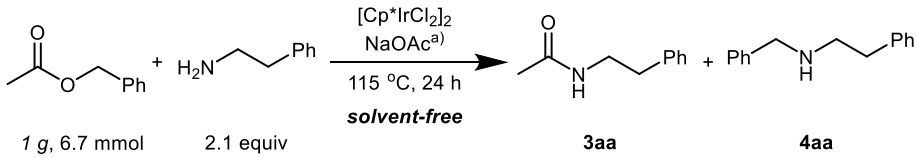
In general, the yields of amide were higher than those of amines. Benzylamines afforded both amides and secondary amines (Table 3.2, entries 2, 9–11). Cyclohexylamine (2e) and cyclopentylamine (2f) also smoothly afforded the corresponding amides and amines (Table 3.2, entries 5 and 6). In contrast, the less basic aniline was not reactive for the synthesis of both amides and amines as reported in other cases (Table 3.2, entry 12). [3a,6d]

Next, the reactions of 2a with different esters were investigated. Benzyl acetates with electron-withdrawing and electron-donating substituents showed similar results in the synthesis of the corresponding amides (Table 3.3, entries 1 and 2). However, benzyl acetate with an electron-donating substituent resulted in slightly lower yields of secondary amine (Table 3.3, entry 2). Benzyl benzoate (1d) was less successful in this reaction than the acetate esters probably because of the steric hindrance (Table 3.3, entry 3).

However, the length of the alkyl chains on the acyl part of esters did not adversely affect the reaction (Table 3.3, entries 4 and 7). The substituents on 1-methylbenzyl acetate (**1f**) and piperonyl acetate (**1g**) interrupted the corresponding amine formation (Table 3.3, entries 5 and 6). n-Hexyl acetate (**1i**) also afforded **3a** and *N*-hexyl-2-phenylethylamine (**6i**) (Table 3.3, entry 8).

Avoidance of organic solvent is an important issue in modern organic synthesis in order to reduce the environmental impact.[9] It is of much benefit for large-scale synthesis. Gratifyingly, our developed conditions could be readily scaled up to gram quantities to obtain **3aa** and **4aa** from **1a** (Table 3.4).[10]

Table 3.4 Gram-scale reaction



$[Cp^*IrCl_2]_2$ (mol%)	3aa (%) b)	4aa (%) b)
1.25	98	71
0.6	92	65
0.5	94	64
0.3	77 c)	17 c)

[a] Equivalents same as that of the iridium catalyst. [b] Isolated yields.
[c] GC yield with dodecane as the internal standard.

It is notable that the reduced catalyst loading showed similar catalytic activity while the reaction with 0.3 mol% of catalyst retarded both the formation of amide and amine.

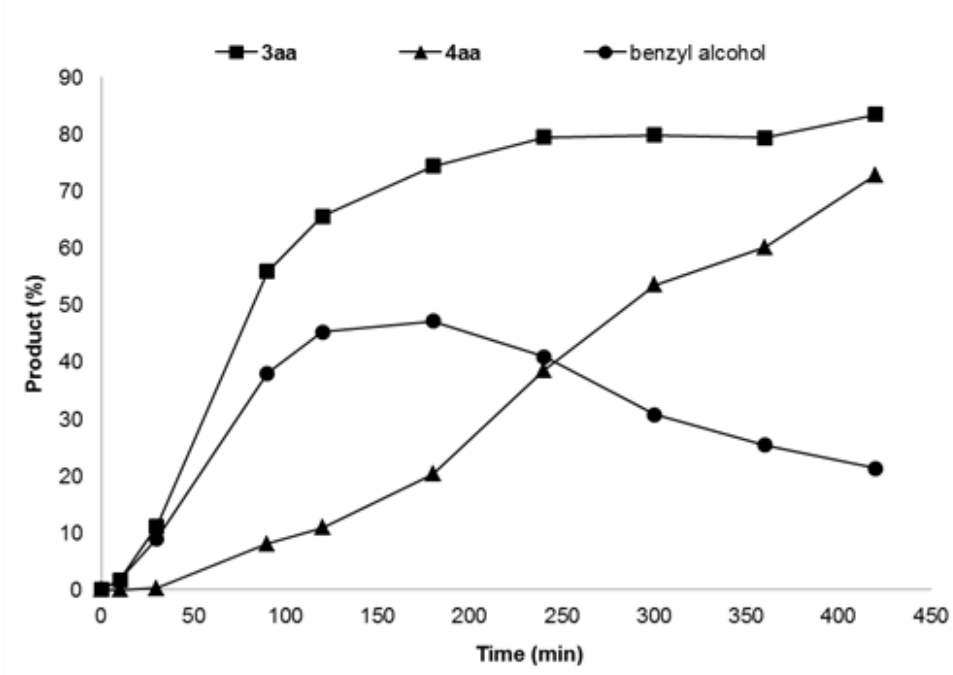
3.2.3 Mechanism study

Next, to gain mechanistic insights into the reaction, a kinetic study was performed by monitoring the progress of the reaction of **1a** with **2a** (Figure 3.1). At the initial stage of the reaction, the rate of the amide formation was very rapid. Benzyl alcohol was detected by gas

chromatography (GC) analysis, indicating that the free alcohol was generated from the ester before forming the secondary amine.

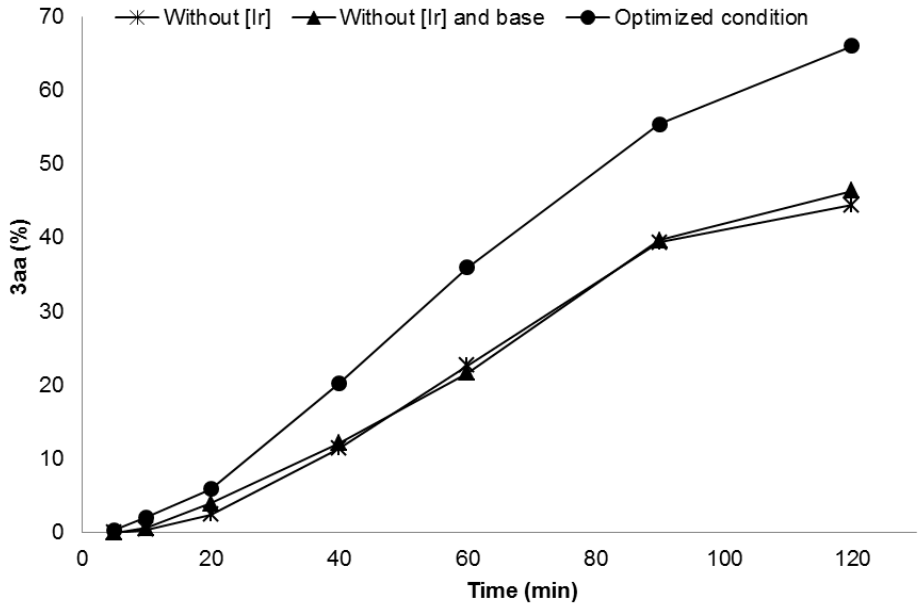
At approximately T=150 min, the rate of **4aa** formation surpassed that of the alcohol formation thereby decreasing the alcohol concentration. We also conducted comparable experiments to probe the reaction profile in absence of iridium and base. As expected, the secondary amine was not detected in the reaction without the iridium complex. Furthermore, it also turned out that amide formation was accelerated by the iridium catalyst from the initial time of the reaction (Figure 3.2).

Figure 3.1 Reaction profile



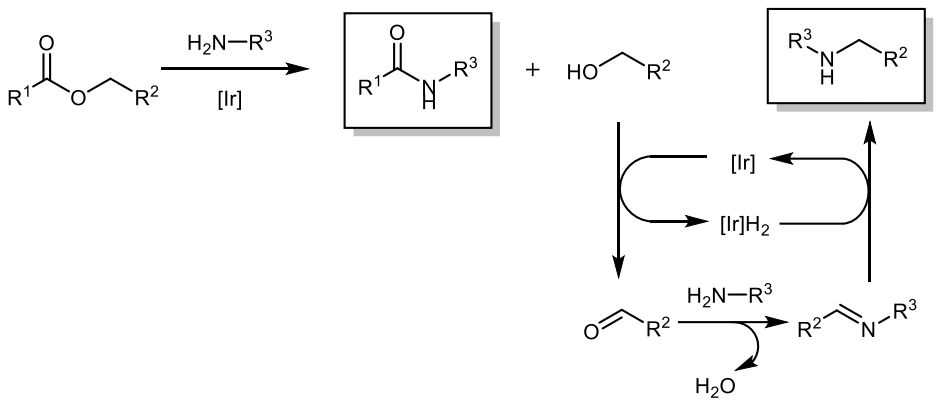
Reaction profile that shows the amount of product formed. Reaction conditions: 1a (0.25 mmol, 1.0 equiv.), **2a** (2.2 equiv.), $[Cp^*IrCl_2]_2$ (1.25 mol%), NaOAc (2.5 mol%), 115 °C. The progress in the reaction was monitored by GC analysis using dodecane as the internal standard.

Figure 3.2 Reaction profile for amide formation



Reaction profile that shows the amount of amide **3aa** formed. **1a** (0.25 mmol, 1.0 equiv), **2a** (2.0 equiv), 115 °C. The progress in the reaction was monitored by GC analysis using dodecane as the internal standard.

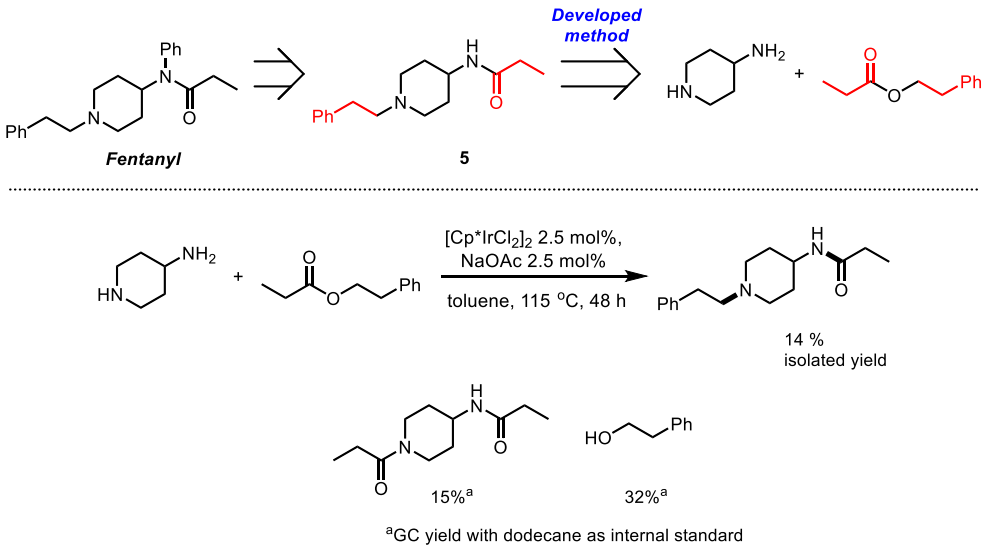
Based on the conducted experiment and previous reports, [6,8,11] a probable mechanism for the $[Cp^*IrCl_2]_2$–catalyzed synthesis of amides and secondary amines from esters is suggested (Scheme 3.2). First, the amide is formed by nucleophilic acyl substitution of the ester with primary amine. Next, the in situ generated alcohol is dehydrogenated and reacts with additional primary amine to form imine. Finally, hydrogenation of imine by hydrogen transfer from the iridium hydride affords the secondary amine.



Scheme 3.2 Proposed mechanism.

3.2.4 Applications

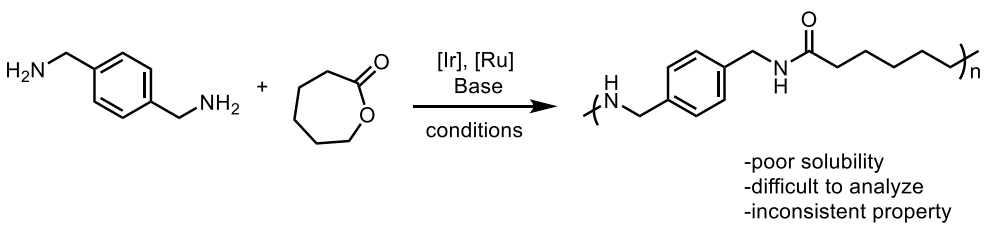
3.2.4.1 Application to the synthesis of Fentanyl



Scheme 3.3 Synthesis of Fentanyl

With a range of reaction conditions established, we were keen to apply our chemistry to a pharmaceutical compound, Fentanyl. Tandem *N*–acylation and *N*–alkylation of 4–aminopiperidine should give a compound **5**, and subsequent *N*–arylation will produce Fentanyl. However, the optimization for the desired reaction step ended up 14% in isolated yield. This result is probably because of the steric hindrance of the substrate.

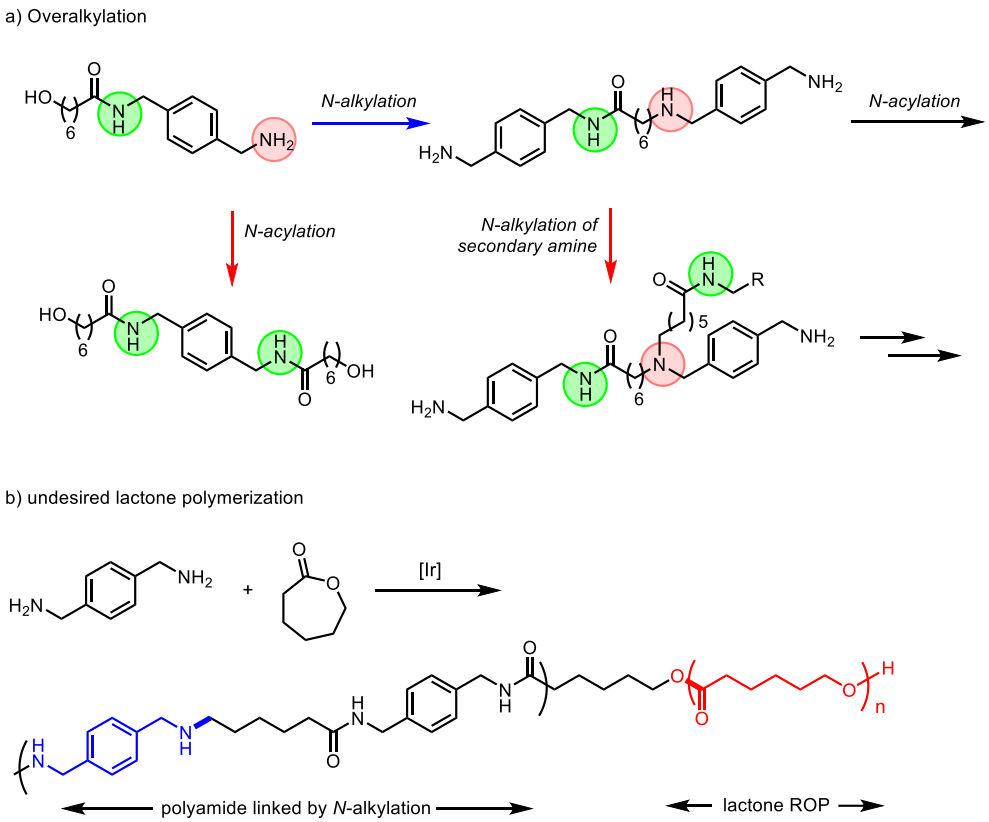
3.2.4.2 Application to polymer synthesis



Scheme 3.4 Synthesis of polyamide

The developed synthetic method was applied to the synthesis of polymer from the reaction between *p*–xylylenediamine and lactone which contains both amide and secondary amine functional groups. We envisioned that lactone ring opening through *N*–acylyation with the one side of amine would furnish free alcohol and *N*–alkylation with another primary amine side. Unfortunately, the resulting products showed very poor solubility making it impossible to analyze.

The undesired over-alkylation led to cross-linked structures which contributed to the poor solubility (Scheme 3.5a). Furthermore, the selectivity of *N*-alkylation over lactone ring opening polymerization could not be controlled under the current system (Scheme 3.5b).



Scheme 3.5 Obstacles to polymerization

3.3 Conclusion

An environmentally-friendly, atom-economic method was developed for synthesizing amides and secondary amines in one-pot using a simple iridium(III) catalytic system under solvent-free conditions, generating water as the sole by-product. Various amides and secondary amines were synthesized efficiently from their corresponding primary amines and esters, even in gram-scale reactions. Notably, the current method utilizes esters as the direct carbon source for both amides and secondary amines.

3.4 Experimental section

3.4.1 General information

Unless otherwise noted, all reactions were carried out using a 4 mL vial in an argon-filled glove box. NMR spectra were recorded in $CDCl_3$ and residue solvent signals were used as a reference. Chemical shifts were reported in ppm and coupling constant in Hz. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet): q (quartet); spt (septet); m (multiplet). All reagents and solvents, unless otherwise noted, were purchased from commercial suppliers and used as received without further purification. Esters

1b–1i were either purchased or synthesized according to the literature.

3.4.2 GC analysis for the reaction profile

Inside an argon–filled glove box, $[Cp^*IrCl_2]_2$ (2.5 mg, 1.25 mol%) and NaOAc (0.5 mg, 2.5 mol%) were added to oven–dried 4 mL vial equipped with septum screw cap. **1a** (36 μL, 0.25 mmol), **2a** (69 μL, 0.55 mmol) were added into the vial using micro–syringe after the vial was taken out of the glove box. The vials were individually prepared for 0 min, 5 min, 10 min, 20 min, 40 min, 60 min, 90 min, 120 min and heated at 115 °C. After the required time, the vial was removed from heating, quickly cooled down under low temperature, diluted wtih dichloromethane and dodecane (22.7 μL, 0.1 mmol) as an internal standard was added to the vial. The sample was filtered with celite before analyzed with GC.

3.4.3 General procedure for amide synthesis

$[Cp^*IrCl_2]_2$ (50 mg, 0.062 mmol), NaOAc (8.0 mg, 0.010 mmol) were added in an oven dried vial inside the glove box. The vial was taken

out and the ester (0.50 mmol) and amine (1.15 mmol) were added under argon atmosphere. The mixture was heated to 115 °C for 24 h before being cooled to room temperature. Purification of the crude product was performed by flash column chromatography. All products were identified by spectral comparison with literature data.

3.4.4 Synthesis of Amides and Secondary Amines with different Primary Amines (Table 3.2)

N-2-(Phenylethyl)acetamide (3aa):[12]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.36-7.20 (m, 5H), 5.52 (bs, 1H), 3.53 (dd, J = 12.9, 6.9 Hz, 2H), 2.83 (t, J = 6.9 Hz, 2H), 1.95 (s, 3H).

N-Benzyl-2-phenethylamine (4aa):[13]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.31-7.15 (m, 10H), 3.78 (s, 2H), 2.90-2.86 (m, 2H), 2.83-2.78 (m, 2H), 1.53 (s, 1H).

N-Benzylacetamide (3ab):[12]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.34-7.24 (m, 5H), 6.09 (bs, 1H), 4.38 (d, J = 5.7 Hz, 2H), 1.98 (s, 3H), 1.24 (s, 1H).

N-Benzyl-1-phenylmethanamine (4ab):[13]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.26-7.16 (m, 10H), 3.73 (s, 4H),

1.65 (s, 1H).

N-(3-Phenylpropyl)acetamide (3ac):[12]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.40-7.31 (m, 2H), 7.30-7.20 (m, 3H), 5.82 (bs, 1H), 3.41 - 3.27 (m, 2H), 2.78-2.62 (m, 2H), 2.00 (s, 3H), 1.91 (dt, J = 14.6, 7.5 Hz, 2H).

N-Benzyl-3-phenylpropan-1-amine (4ac):[14]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.28-7.10 (m, 10H), 3.73 (s, 2H), 2.64-2.59 (m, 4H), 1.82-1.78 (m, 2H), 1.50 (s, 1H).

N-Heptylacetamide (3ad):[15]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 5.74 (bs, 1H), 3.26-3.12 (m, 2H), 1.94 (s, 3H), 1.50-1.40 (m, 2H), 1.30-1.21 (m, 8H), 0.85 (t, J = 6.7 Hz, 3H).

N-Benzylheptan-1-amine (4ad):[16]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.27-7.19 (m, 5H), 3.73 (s, 2H), 2.57

(t, J = 7.2 Hz, 2H), 1.55 (s, 1H), 1.48–1.43 (m, 2H), 1.25–1.23 (m, 8H), 0.82 (t, J = 6.5 Hz, 2H).

N–Cyclohexylacetamide (3ae):[17]

^{1}H NMR (300 MHz, $CDCl_3$, δ): δ 5.57 (bs, 1H), 3.74–3.68 (m, 1H), 1.94 (s, 3H), 1.92–1.86 (m, 2H), 1.75–1.49 (m, 3H), 1.42–1.21 (m, 2H), 1.20–0.97 (m, 3H).

N–Benzylcyclohexanamine (4ae):[18]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.36–7.11 (m, 5H), 3.76 (s, 2H), 2.52–2.37 (m, 1H), 1.87 (d, J = 11.3 Hz, 2H), 1.74–1.62 (m, 2H), 1.60–1.43 (m, 2H), 1.29–0.99 (m, 5H).

N–Cyclopentylamide (3af):[17]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.80 (bs, 1H), 4.22–4.10 (m, 1H), 1.99–1.93 (m, 2H), 1.91 (s, 3H), 1.68–1.59 (m, 2H), 1.59–1.49 (m, 2H), 1.34 (td, J = 12.8, 6.5 Hz, 2H).

N-Benzylcyclopentanamine (4af):[19]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.26-7.16 (m, 5H), 3.71 (s, 2H), 3.05 (p, J = 6.7 Hz, 1H), 1.83-1.75 (m, 2H), 1.68-1.59 (m, 2H), 1.51-1.42 (m, 2H), 1.32 (td, J = 14.0, 7.8 Hz, 2H), 0.39 (s, 1H).

N-(4-Methoxyphenethyl)acetamide (3ag):[20]

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.10 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.54 (bs, 1H), 3.78 (s, 3H), 3.50-3.42 (m, 2H), 2.74 (t, J = 7.0 Hz, 2H), 1.93 (s, 3H).

N-(4-Methoxyphenethyl)benzylamine (4ag):[21]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.31-7.15 (m, 5H), 7.09 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.77 (s, 2H), 3.75 (s, 3H), 2.89-2.80 (m, 2H), 2.79-2.69 (m, 2H), 1.52 (s, 1H).

N-(3-Fluorophenethyl)acetamide (3ah):[22]

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.29-7.25 (m, 2H), 6.98-6.88 (m, 3H), 5.44 (bs, 1H), 3.53-3.49 (m, 2H), 2.82 (t, J = 7.0 Hz, 2H), 1.95 (s, 3H).

N-(3-Fluorophenethyl)benzylamine (4ah):

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.30-7.21 (m, 6 H), 6.99 (d, J = 7.3 Hz, 1 H), 6.97-6.87 (m, 2 H), 3.81 (s, 2 H), 2.93 (t, J = 6.8 Hz, 1 H), 2.84 (t, J = 6.8 Hz, 2 H), 1.47 (s, 1H).

^{13}C NMR (126MHz, $CDCl_3$, δ): 162.9 (d, J = 245.1 Hz), 142.5 (d, J = 7.23 Hz), 140.0, 129.8 (d, J = 8.6 Hz), 128.4, 128.0, 126.9, 124.3 (d, J = 2.9 Hz), 115.5 (d, J = 20.98 Hz), 113.0 (d, J = 20.98 Hz), 53.8, 50.1, 36.0. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −113.58 ppm; HRMS-FAB (m/z) [M+H]+ calcd for $C_{15}H_{17}FN$, 230.1347; found: 230.1345.

N-(4-Methylbenzyl)acetamide (3ai):[12]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.19-7.13 (m, 4H), 5.85 (bs, 1H), 4.38 (d, J = 5.6 Hz, 2H), 2.34 (s, 3H), 2.01 (s, 3H).

N-(4-Methylbenzyl)benzylamine (4ai):[23]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.40-7.18 (m, 9H), 3.89-3.81 (m, 4H), 2.39 (s, 3H), 1.76 (s, 1H).

N-(4-Methoxybenzyl)acetamide (3aj):[12]

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.19 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 5.97 (bs, 1H), 4.33 (d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 1.98 (s, 3H).

N-(4-Methoxybenzyl)benzylamine (4aj):[19]

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.28-7.22 (m, 4H), 6.81 - 6.78 (m, 3H), 6.79 (d, J = 8.7 Hz, 2H), 3.72 (s, 5H), 3.67 (s, 2H), 1.76 (s, 1H).

N-(4-Chlorobenzyl)acetamide (3ak):[12]

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.28 (d, J = 6.8 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 5.89 (bs, 1H), 4.37 (d, J = 5.1 Hz, 2H), 2.01 (s, J = 3.8 Hz, 3H).

N-(4-Chlorobenzyl)benzylamine (4ak):[24]

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.35-7.19 (m, 9H), 3.76-3.71 (m, 4H), 1.61 (s, 1H).

N–Phenylacetamide (3al):[25]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.50 (d, J=7.8 Hz, 2 H), 7.33 (t, J=8.0 Hz, 2 H), 7.07–7.16 (m, 1 H), 2.19 ppm (s, 3 H)

N–Benzylaniline (4al):[6b]

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.34–7.41 (m, 4 H), 7.27–7.32 (m, 1 H), 7.18 – 7.23 (m, 2 H), 6.74 – 6.79 (m, 1 H), 6.68 (dd, J=8.8, 1.0 Hz, 2 H), 4.35 ppm (s, 2 H).

3.4.5 Synthesis of Amides and Secondary Amines with different Esters (Table 3.3)

N-(4-Chlorobenzyl)phenethylamine (4ba):[26]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.32-7.19 (m, 9H), 3.77 (s, 2H), 2.91-2.79 (m, 4H), 1.52 (s, 1H).

N-(4-Methoxybenzyl)phenethylamine (4ca):[26]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.31-7.10 (m, 5H), 7.09 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.77 (s, 2H), 3.75 (s, 3H), 2.87-2.82 (m, 2H), 2.77-2.72 (m, 2H), 1.52 (s, 1H).

N-Phenethylbenzamide (3da):[12]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.70 (d, 2H), 7.47-7.22 (m, 8H), 6.33 (bs, 1H), 3.74-3.67 (m, 2H), 2.93 (t, J = 7.0 Hz, 2H).

N-Phenethylpropionamide (3ea):[27]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.26-7.10 (m, 5H), 5.50 (bs, 1H),

3.44 (m, 2H), 2.74 (t, J = 7.0 Hz, 2H), 2.08 (q, J = 7.6 Hz, 2H), 1.04 (t, J = 7.6 Hz, 3H).

N-(1-Methylbenzyl)phenethylamine (4fa):[7a]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.33-7.13 (m, 10H), 3.78 (q, J = 6.6 Hz, 1H), 2.81-2.68 (m, 4H), 1.33 (d, J = 6.6 Hz, 3H).

N-(2-Phenylethyl)-1,3-benzodioxole-5-methanamine (4ga):

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.31-7.17 (m, 5H), 6.79 (s, 1H), 6.71-6.73 (m, 2H), 5.91 (s, 2H), 3.70 (s, 2H), 2.92-2.85 (m, 2H), 2.84-2.77 (m, 2H), 1.52 (s, 1H).

^{13}C NMR (75MHz, $CDCl_3$, 147.6, 146.4, 140.0, 134.2, 128.7, 128.4, 126.1, 121.1, 108.6, 108.0, 100.8, 53.6, 50.3, 36.3. HRMS-FAB (m/z) [M+H]+ calcd for $C_{16}H_{18}NO_2$, 256.1339; found: 256.1338.

N-Phenethyl-4-phenylbutanamide (3ha):[28]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.32-7.14 (m, 10H), 5.53 (bs, 1H), 3.56-3.50 (m, 2H), 2.80 (t, J = 7.0 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 2.11 (t, J = 7.6 Hz, 2H), 2.01-1.86 (m, 2H).

N-Hexylbenzeneethanamine (4ia):[29]

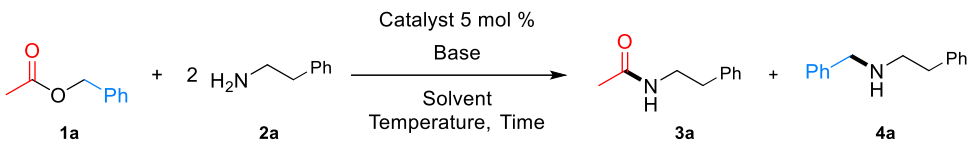
^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.34-7.24 (m, 5H), 3.34-3.28 (m, 2H), 3.25-3.11 (m, 2H), 3.04-2.90 (m, 2H), 2.02-1.87 (m, 2H), 1.64 (bs, 1H), 1.43-1.33 (m, 2H), 1.33-1.24 (m, 4H), 0.84 (t, J = 6.6 Hz, 3H), 1.63 (s, 1H).

N-(2-Phenylethyl)-*N*-(phenylmethyl)-benzeneethan-amine (5aa):[30]

^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.42-7.18 (m, 15H), 3.72 (s, 2H), 2.86 (m, 8H).

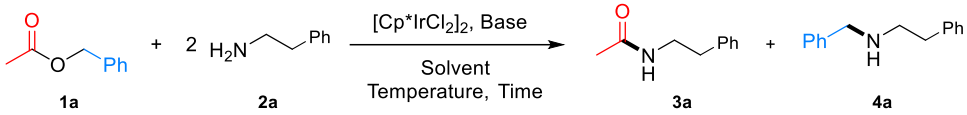
3.4.6 Complementary reaction optimization table

Table 3.5 Optimization table



Entry	Catalyst	Base (mol %)	Solvent	Time	Yield of **3**[a]	Yield of **4**[a]
1	$[(1,5-COD)IrCl]_2$	K_2CO_3 (10 mol %)	Xylene/ 145 °C	36 h	41%	9%
2	$Ir(CO)Cl(PPh_3)_2$	K_2CO_3 (10 mol %)	Xylene/ 145 °C	36 h	98%	16%
3	$IrH(CO)(PPh_3)_3$	K_2CO_3 (10 mol %)	Xylene/ 145 °C	36 h	63%	27%
4	$[Ir(cyclooctene)_2Cl]_2$	K_2CO_3 (20 mol %)	Xylene/ 145 °C	24 h	78%	4%
5	$[Ir_2(cod)_2(OMe)]$	K_2CO_3 (20 mol %)	Xylene/ 145 °C	24 h	30%	22%
6	$Ir(Pyridine)_3Cl_3$	K_2CO_3 (20 mol %)	Xylene/ 145 °C	24 h	88%	5%
7	$IrCl_3$	K_2CO_3 (20 mol %)	Xylene/ 145 °C	24 h	76%	5%
8	$[Ru(p-cymene)Cl_2]_2$ /DPPF (5 mol %)	K_2CO_3 (10 mol %)	Toluene/ 115 °C	36 h	64%	4%
9	$[Ru(p-cymene)Cl_2]_2$ /DPPF (5 mol %)	K_2CO_3 (10 mol %)	Xylene/ 145 °C	24 h	50%	24%
10	$[Ru(benzene)Cl_2]_2$ /DPPF (5 mol %)	K_2CO_3 (10 mol %)	Toluene/ 115 °C	36 h	60%	26%
11	$[Ru(benzene)Cl_2]_2$ /DPPP (5 mol %)	K_2CO_3 (10 mol %)	Xylene/ 145 °C	48 h	67%	17%
12	$Ru(cod)Cl_2$(5 mol %) /DPPF (5 mol %)	K_2CO_3 (20 mol %)	Toluene/ 115 °C	24 h	73%	6%

Table 3.6 Activity of $[Cp^*IrCl_2]_2$



Entry	Catalyst	mol %	Base (mol %)	Solvent	Time	Yield of 1[a]	Yield of 2[a]
1	$[Cp^*IrCl_2]_2$	2.5 mol %	none	Toluene/ 115 °C	24 h	23%	15%
2	$[Cp^*IrCl_2]_2$	2.5 mol %	K_2CO_3 (5 mol%)	Toluene/ 115 °C	36 h	81 %	38 %
3	$[Cp^*IrCl_2]_2$	2.5 mol %	K_2CO_3 (10 mol%)	Toluene/ 115 °C	36 h	80 %	44%
4	$[Cp^*IrCl_2]_2$	2.5 mol %	K_2CO_3 (10 mol%)	Xylene/ 145 °C	36 h	60%	31%
5	$[Cp^*IrCl_2]_2$	2.5 mol %	Na_2CO_3 (5 mol%)	Toluene/ 115 °C	36 h	62 %	46 %
6	$[Cp^*IrCl_2]_2$	2.5 mol %	$NaHCO_3$ (5 mol%)	Toluene/ 115 °C	36 h	69 %	57 %
7	$[Cp^*IrCl_2]_2$	2.5 mol %	Cs_2CO_3 (5 mol%)	Toluene/ 115 °C	36 h	63 %	52 %
8	$[Cp^*IrCl_2]_2$	2.5 mol %	NaOMe (5 mol%)	Toluene/ 115 °C	36 h	90 %	73 %
9	$[Cp^*IrCl_2]_2$	2.5 mol %	NaOMe (2 mol%)	Toluene/ 115 °C	36 h	73%	48%
10	$[Cp^*IrCl_2]_2$	1.25 mol %	NaOAc (2.5 mol%)	Neat/ 115 °C	36 h	99%	73%
11	$[Cp^*IrCl_2]_2$	1.25 mol %	NaOAc (2.5 mol%)	Neat/ 115 °C	24 h	99%	77%
12	$[Cp^*IrCl_2]_2$	2.5 mol %	NaOAc (4 mol%)	Toluene/ 115 °C	36 h	99%	48%
13	$[Cp^*IrCl_2]_2$	1 mol %	NaOAc (1 mol%)	Toluene/ 115 °C	36 h	81%	26%

3.5 Reference

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(10) N-(2-Phenylethyl)-N-(phenylmethyl)-benzeneethanamine 5aa was observed as a byproduct (7% in the case of 1.25 mol% catalyst loading).

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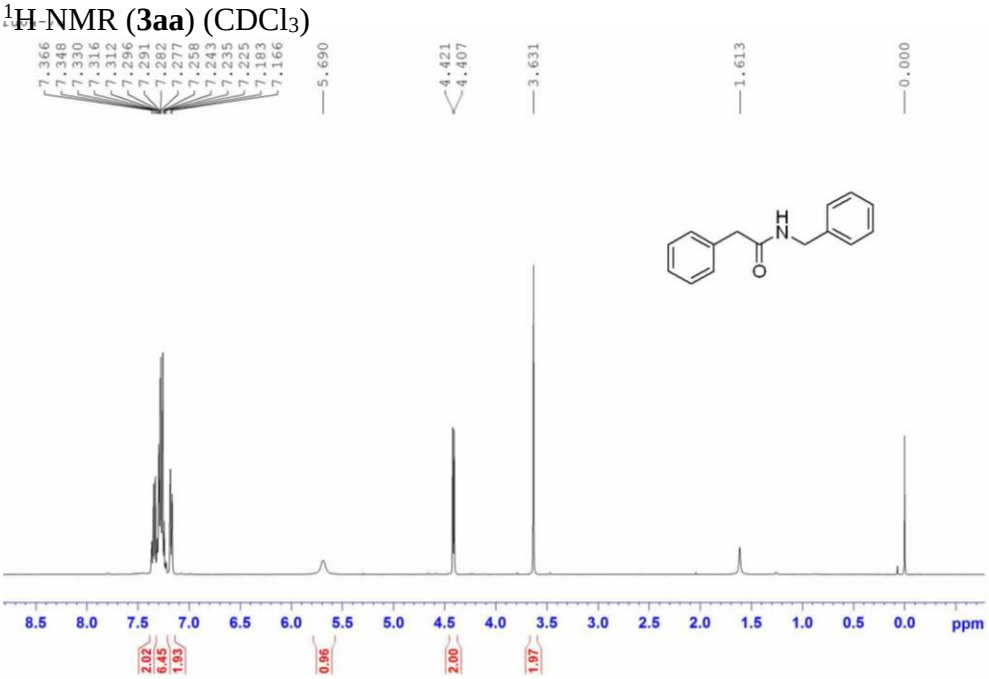
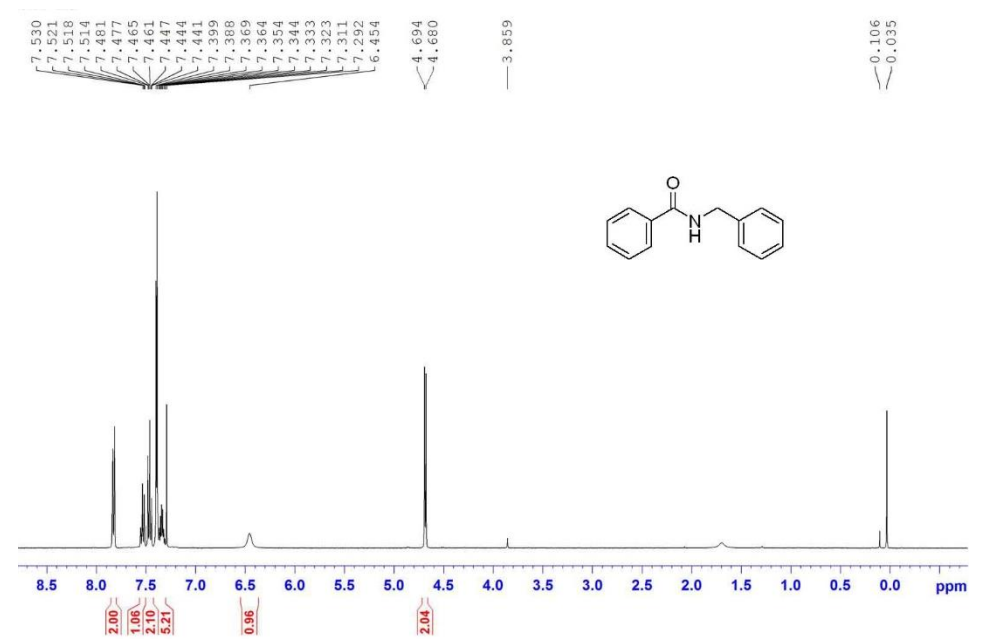
Appendix – NMR spectra

Chapter 2

^{1}H NMR (**3aa**) ($CDCl_3$)



^{1}H NMR (**3ba**) ($CDCl_3$)



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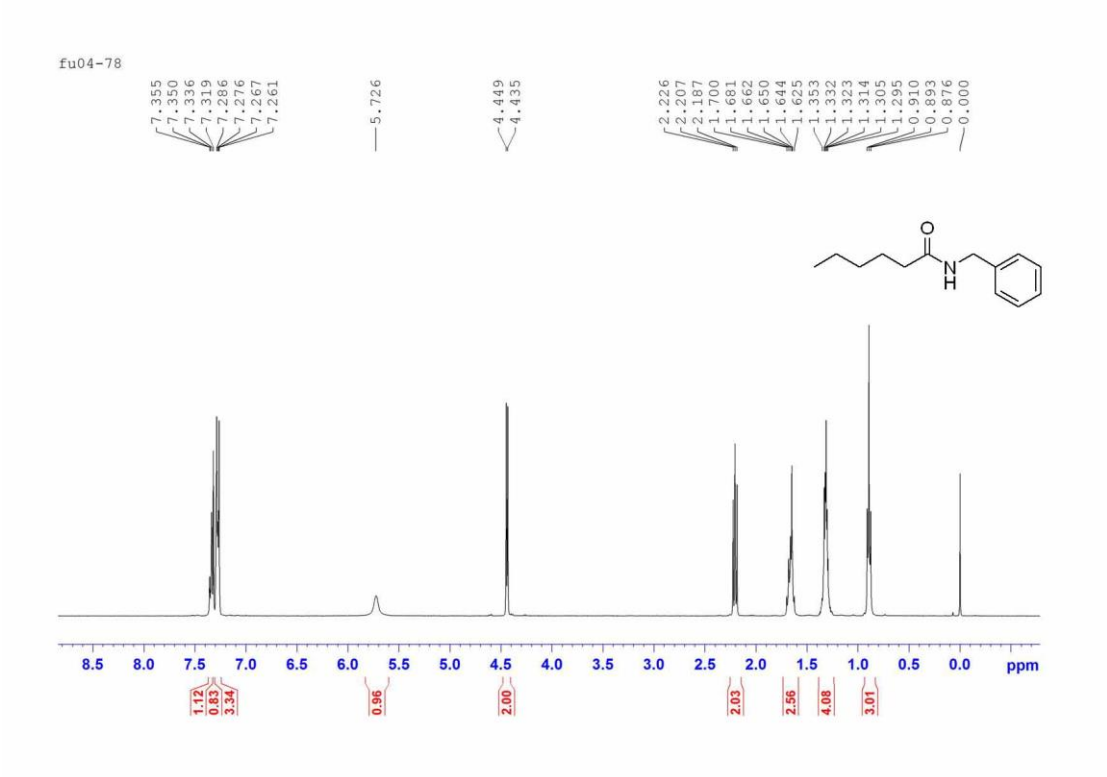

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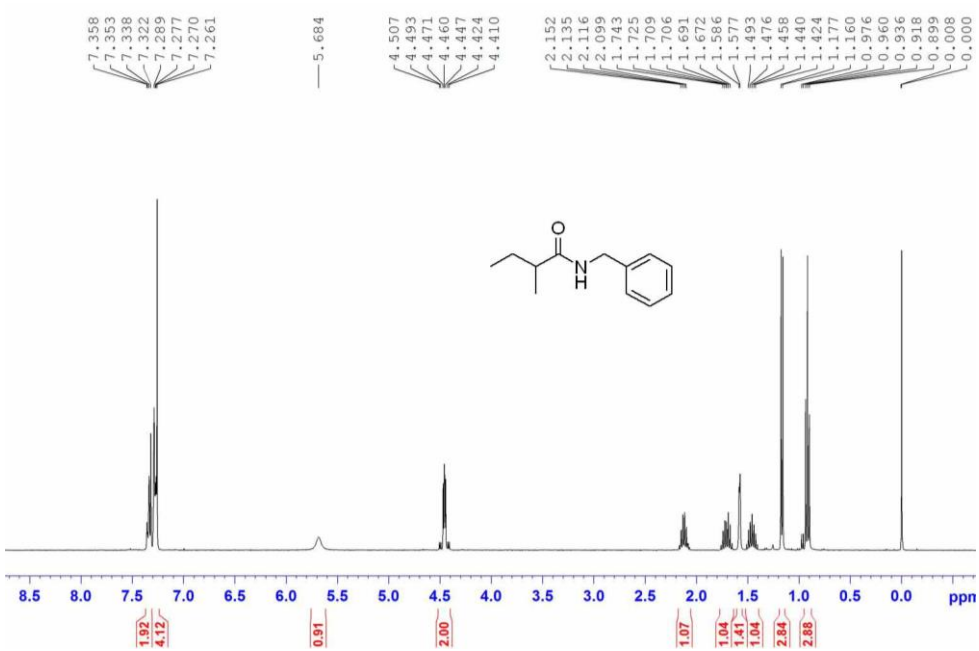

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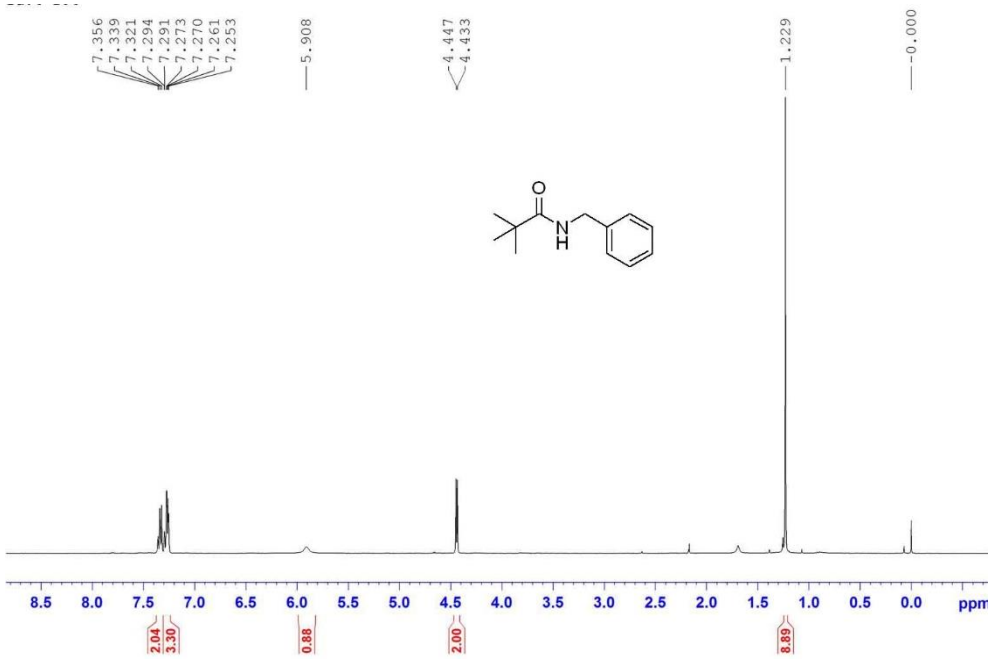
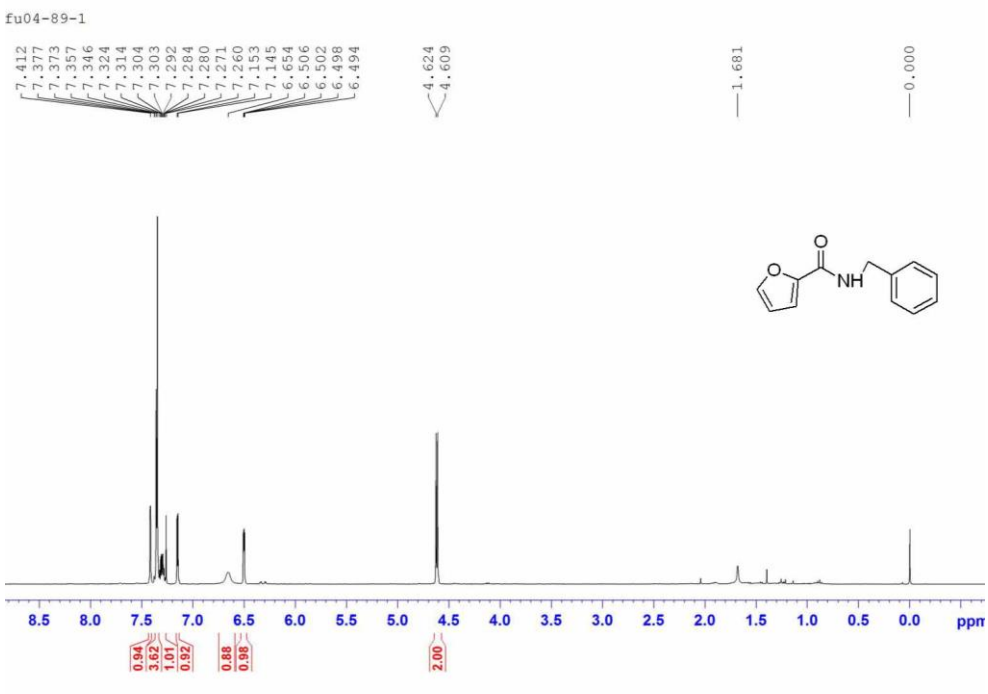
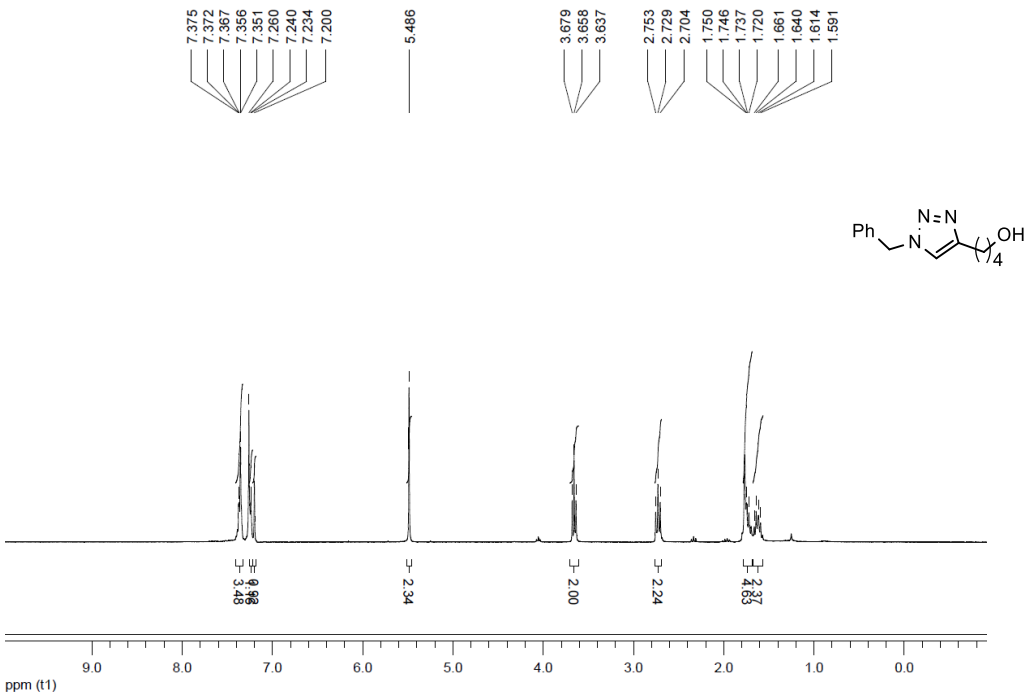


^{1}H NMR (**3fa**) ($CDCl_3$)



^{1}H NMR (**3ha**) ($CDCl_3$)



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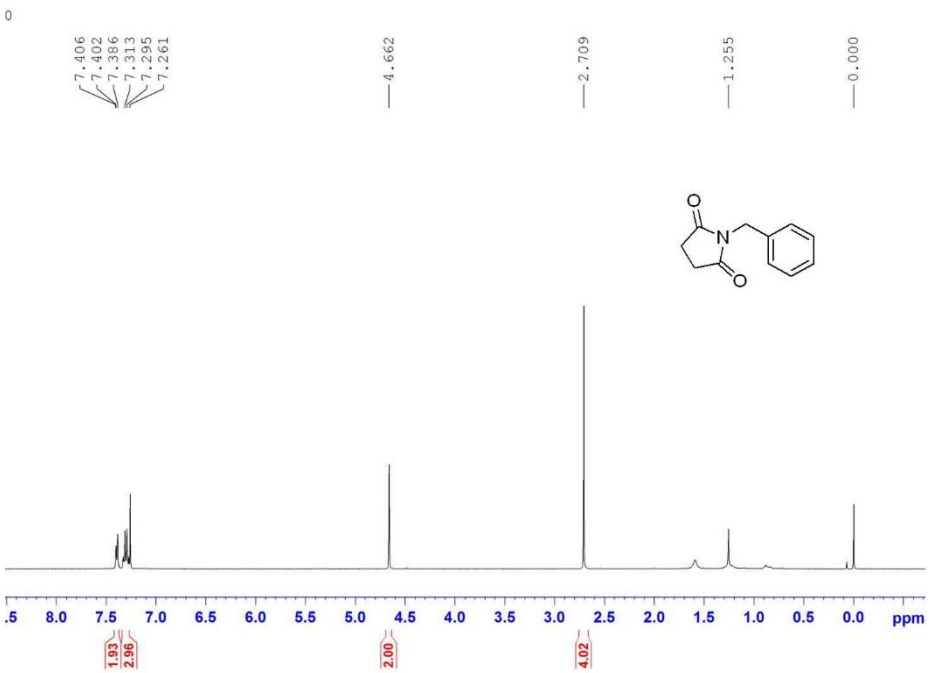
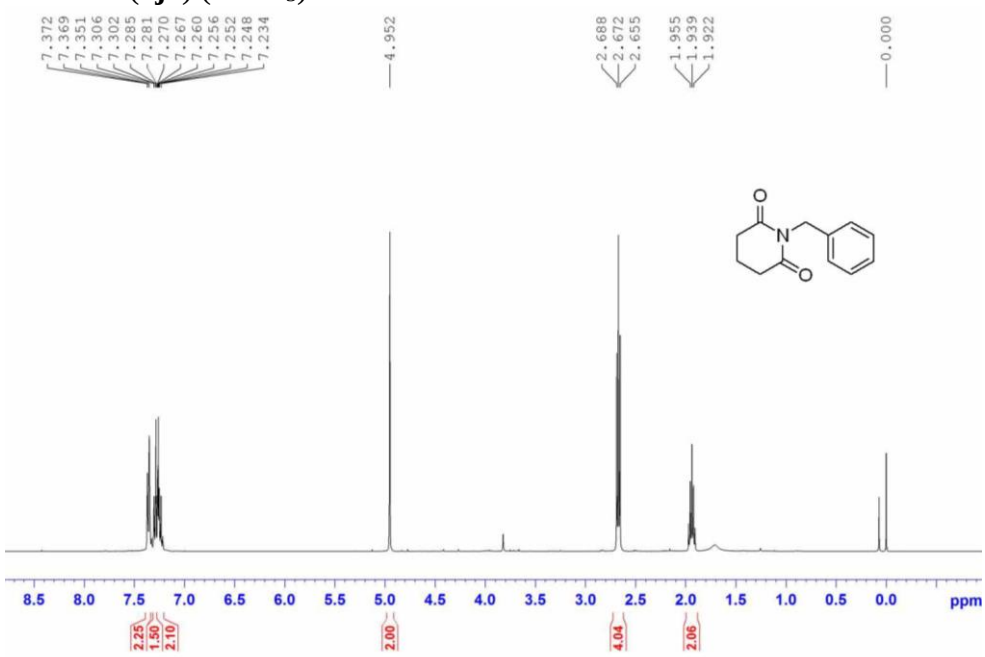


^{1}H NMR (**3ja**) ($CDCl_3$)



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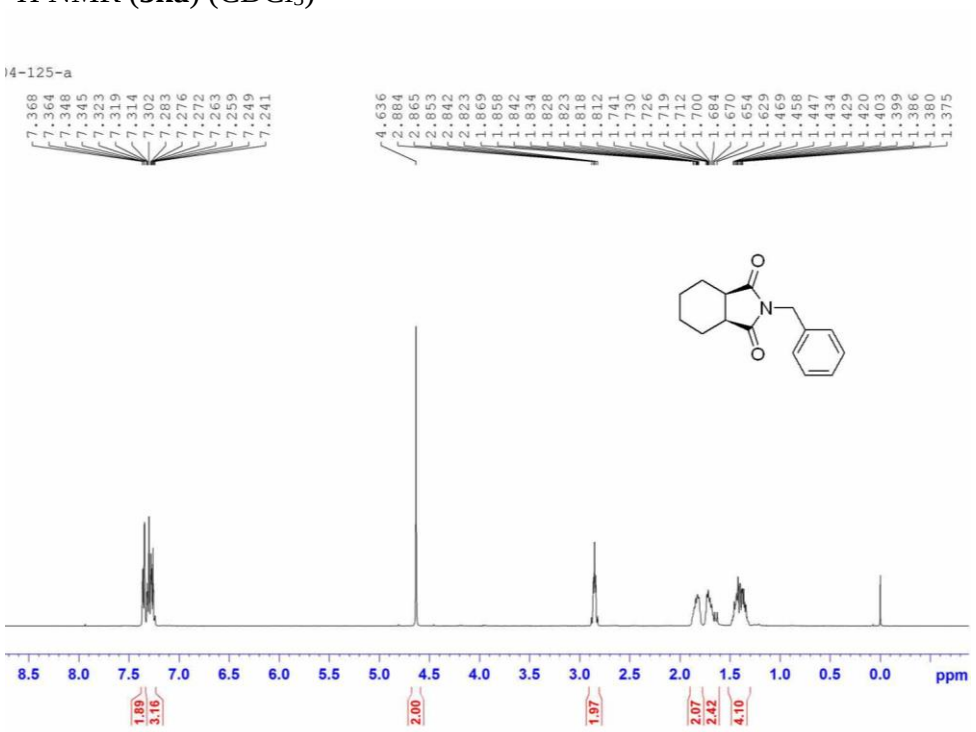

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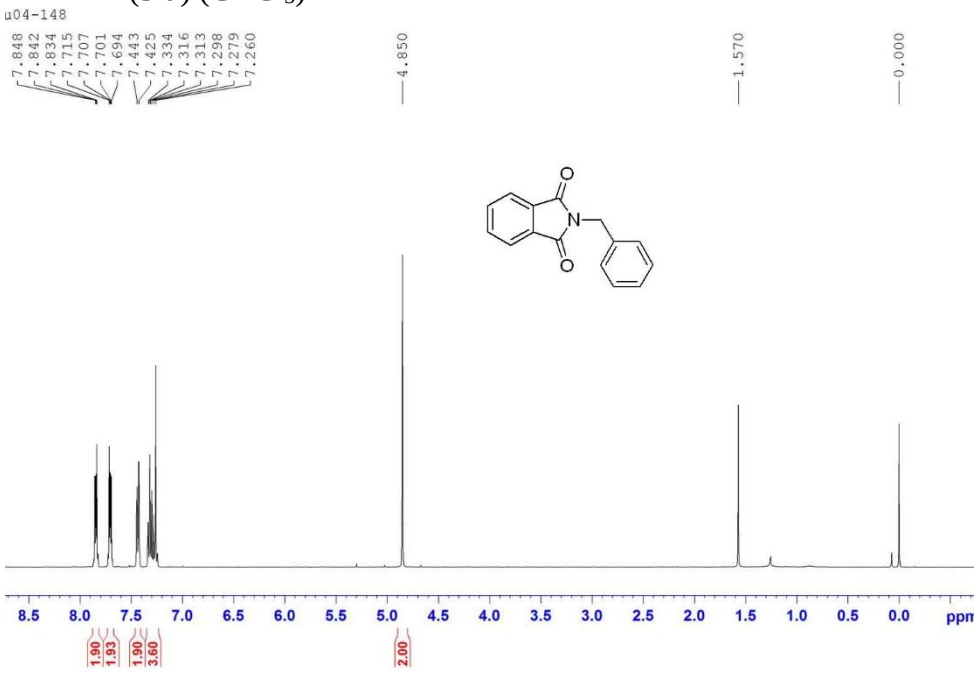

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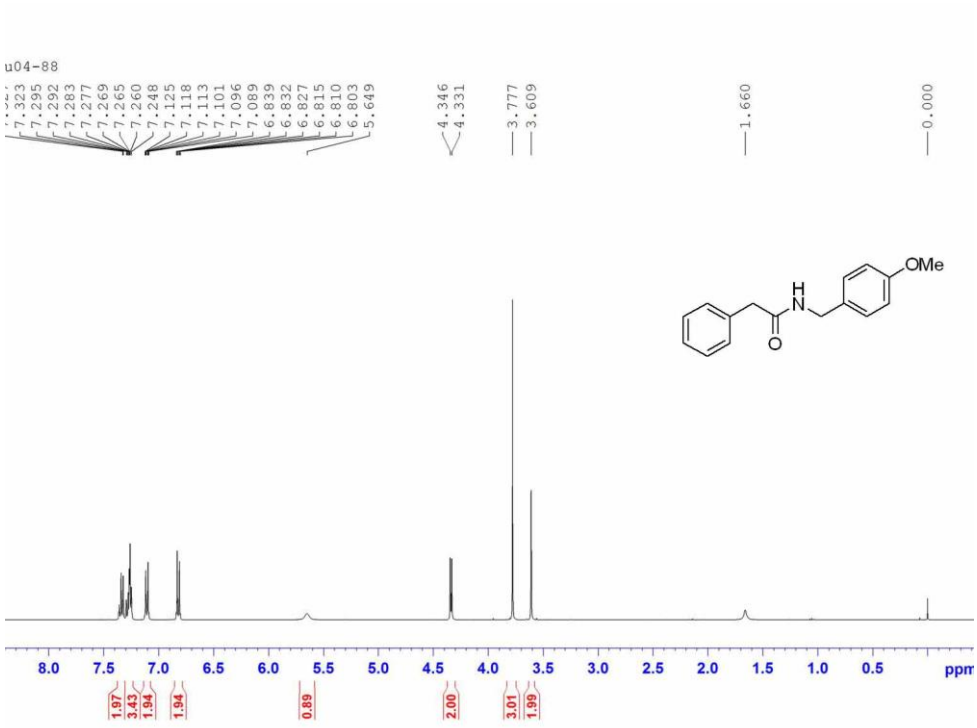
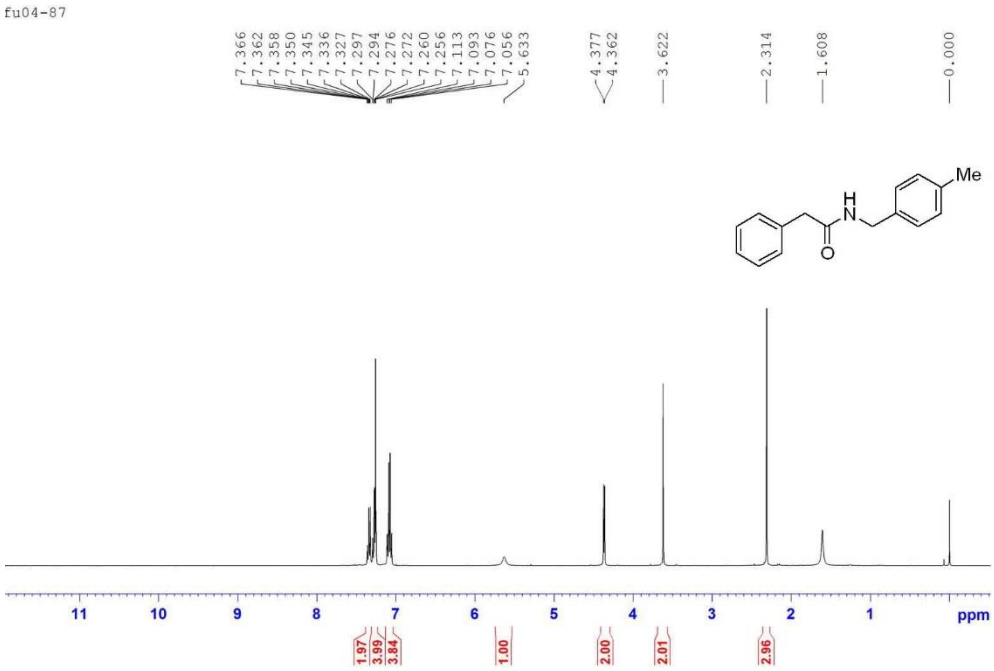
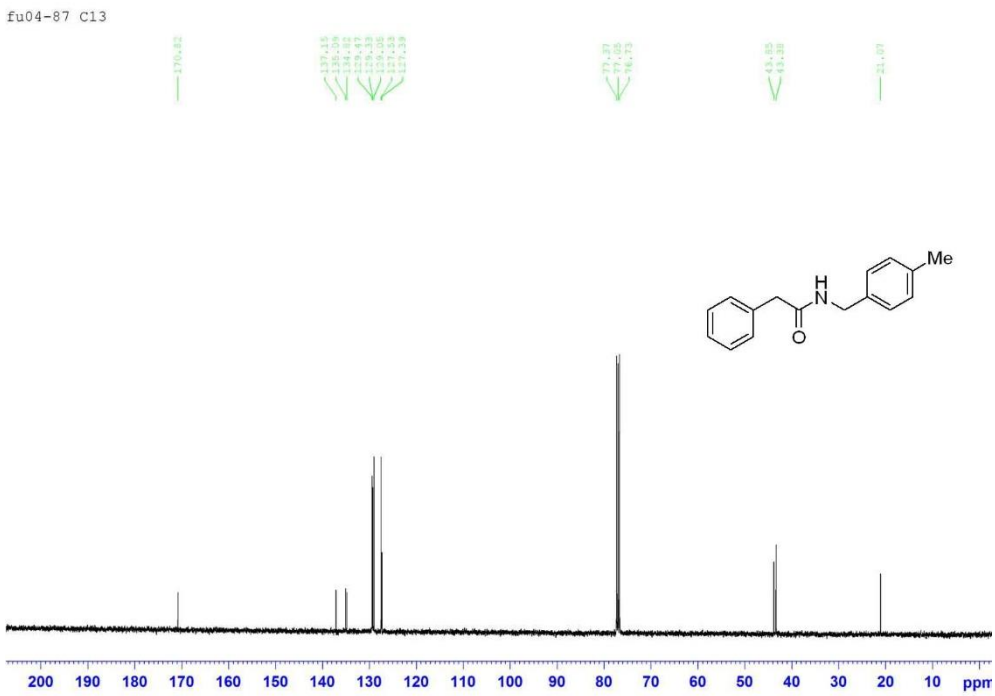


^{1}H NMR (**3ac**) ($CDCl_3$)



^{13}C NMR (**3ac**) ($CDCl_3$)



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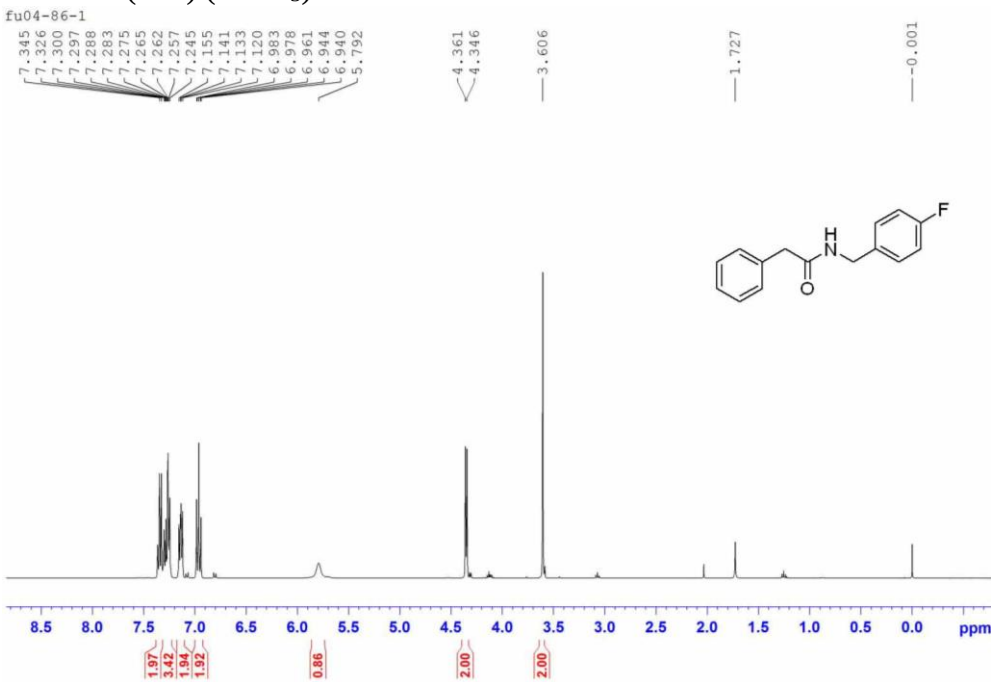
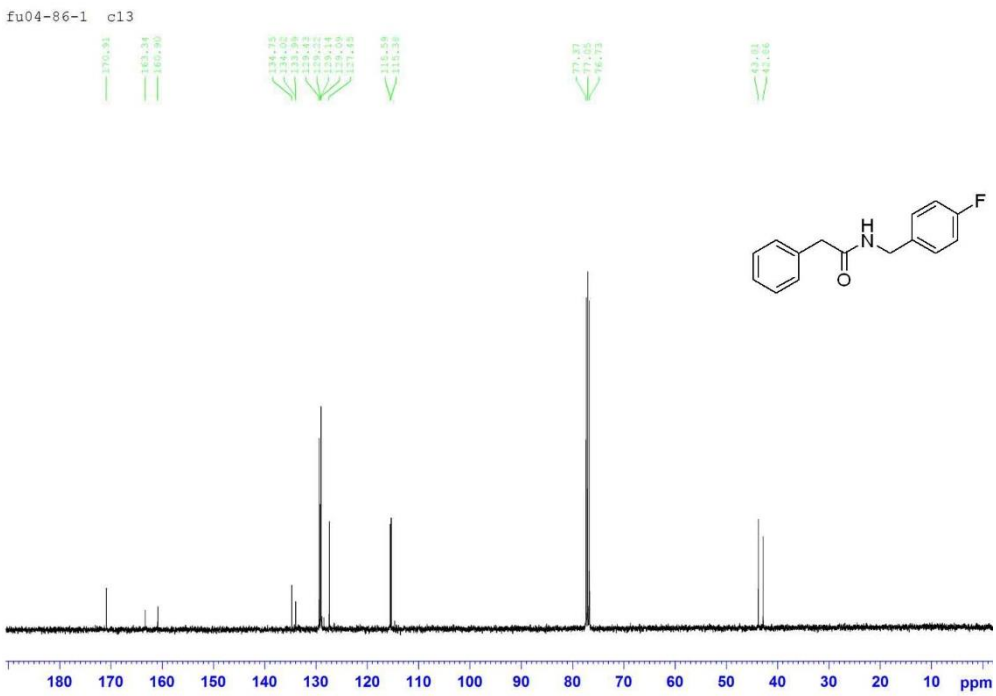
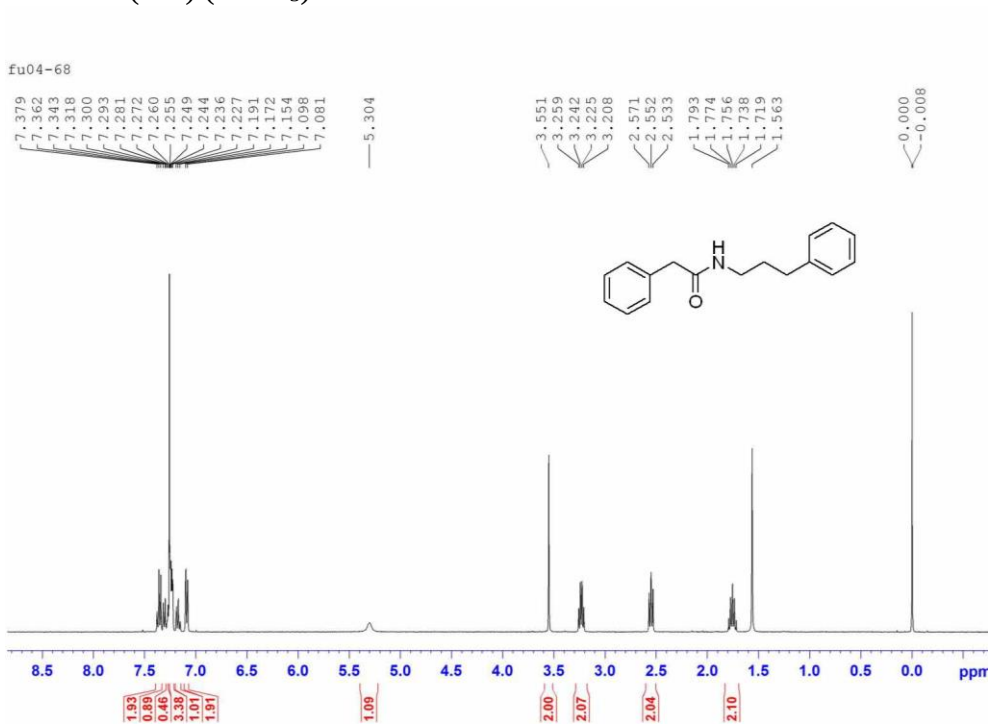


^{13}C NMR (**3ad**) ($CDCl_3$)



^{1}H NMR (**3ae**) ($CDCl_3$)



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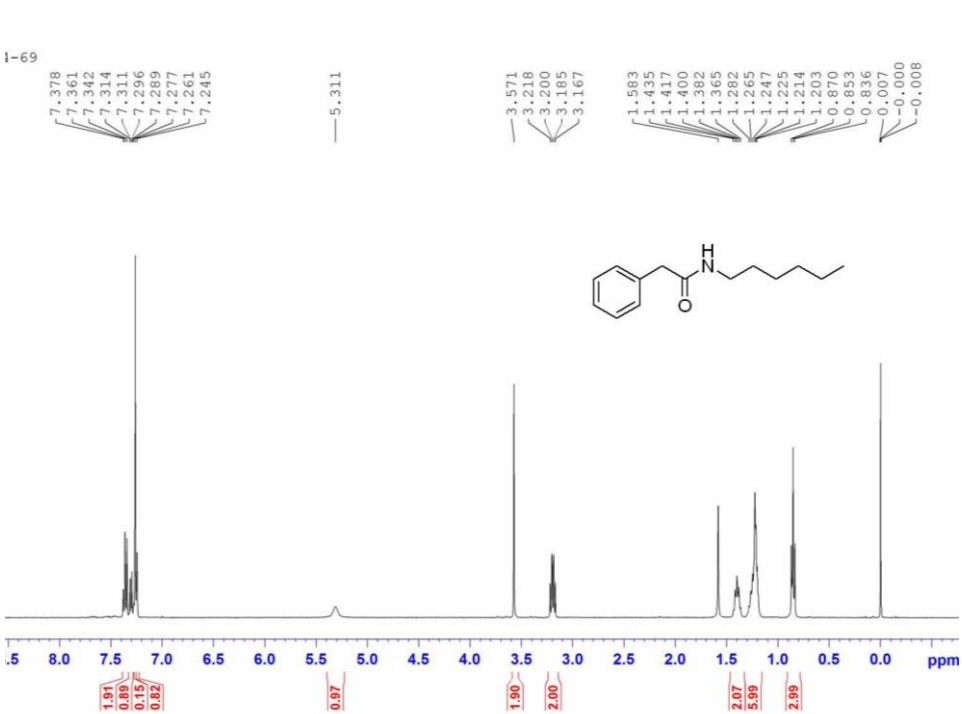
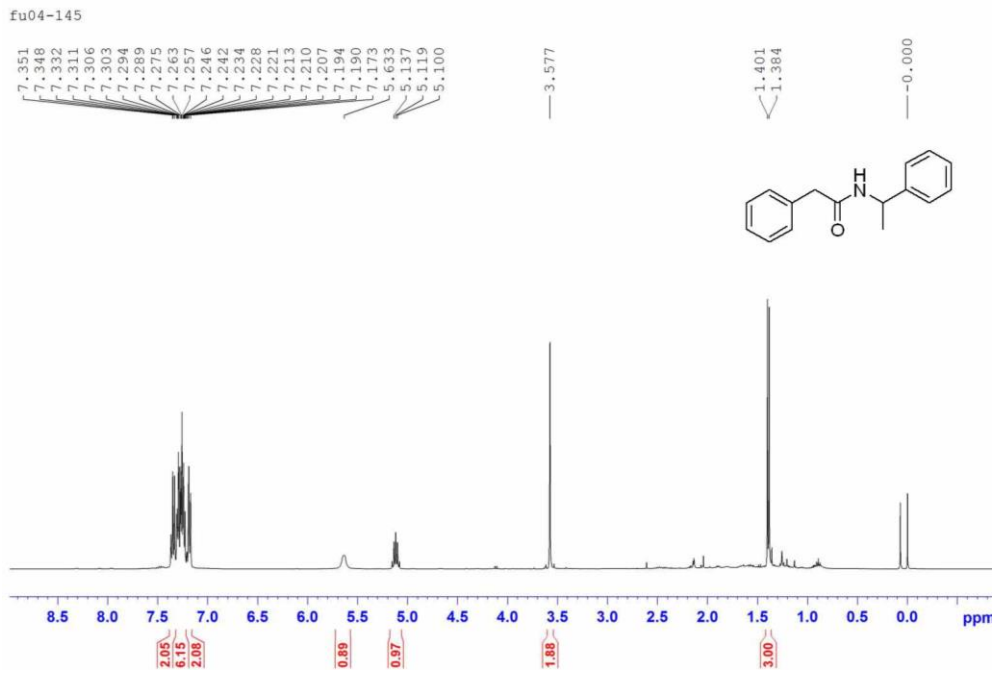
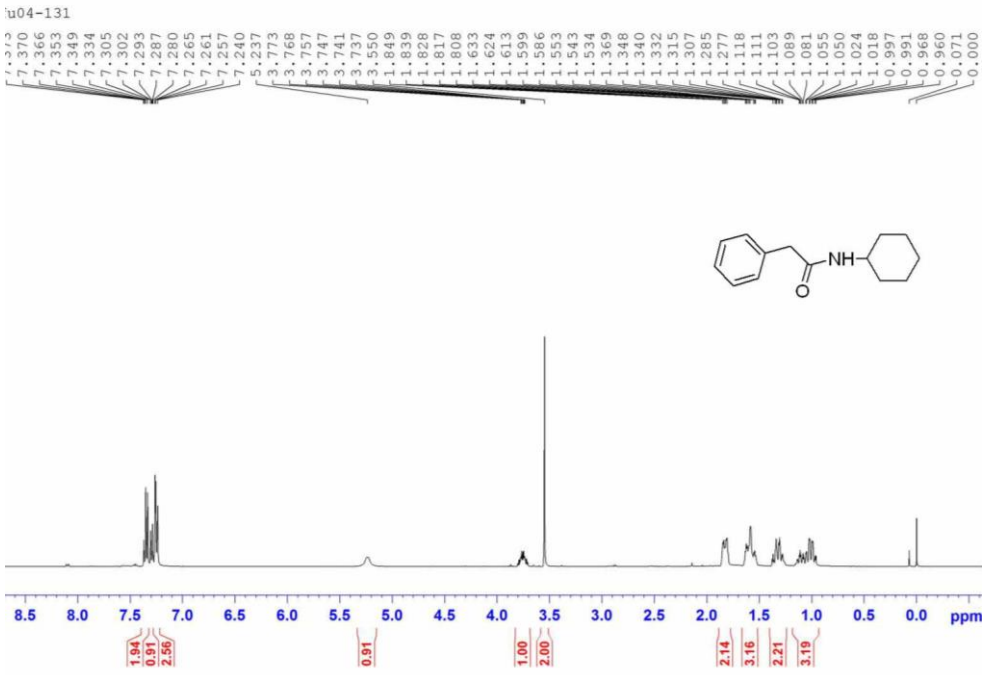


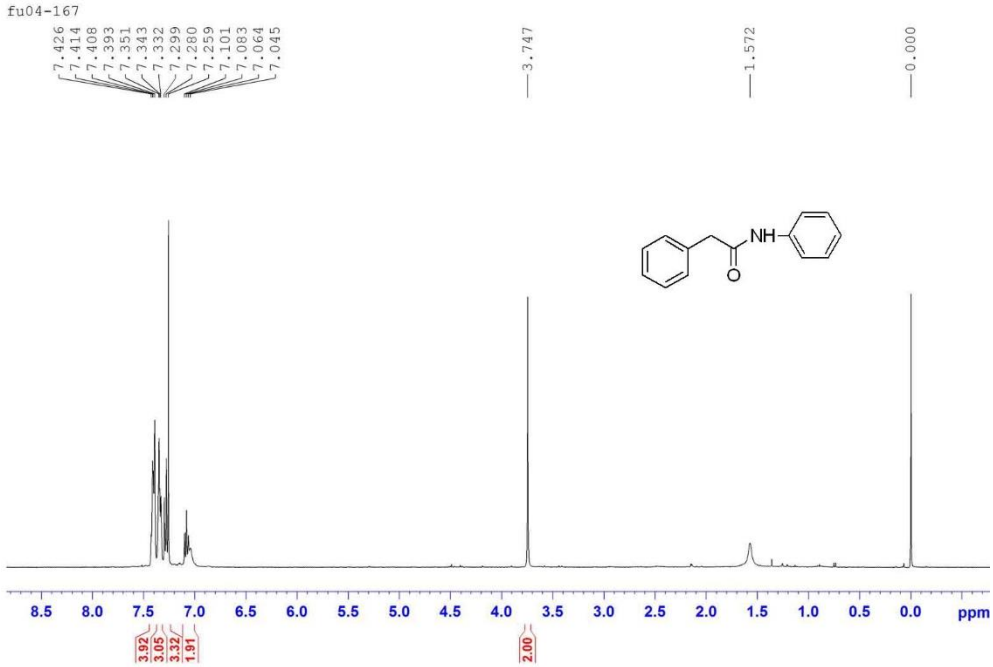
^{1}H NMR (**3ag**) ($CDCl_3$)



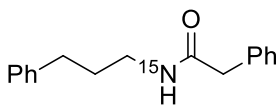
^{1}H NMR (**3ah**) ($CDCl_3$)

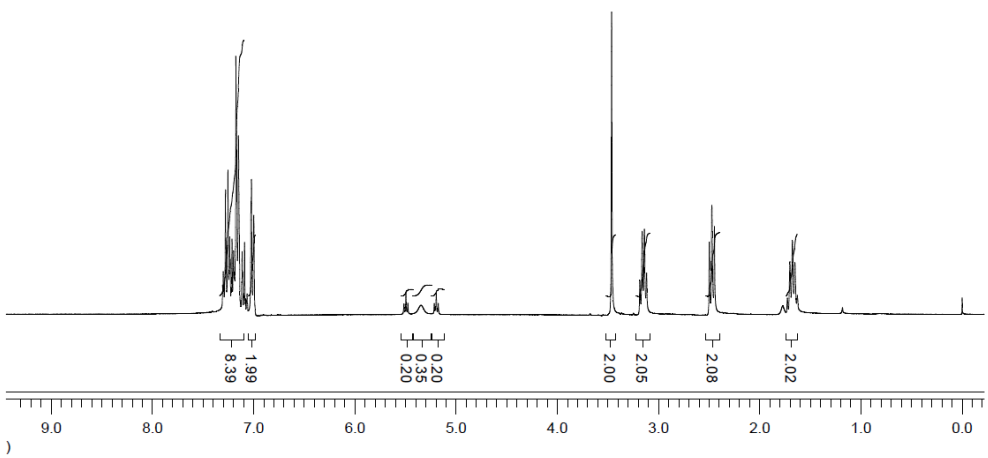


^{1}H NMR (**3ai**) ($CDCl_3$)

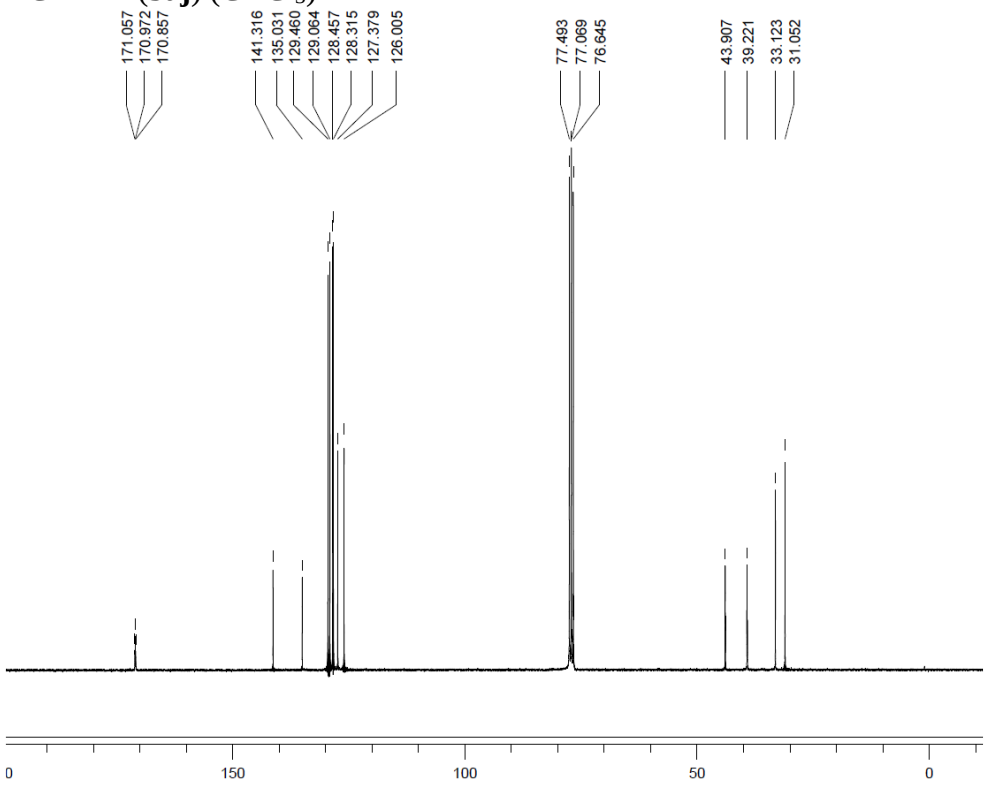


^{1}H NMR (**3aj**) ($CDCl_3$)

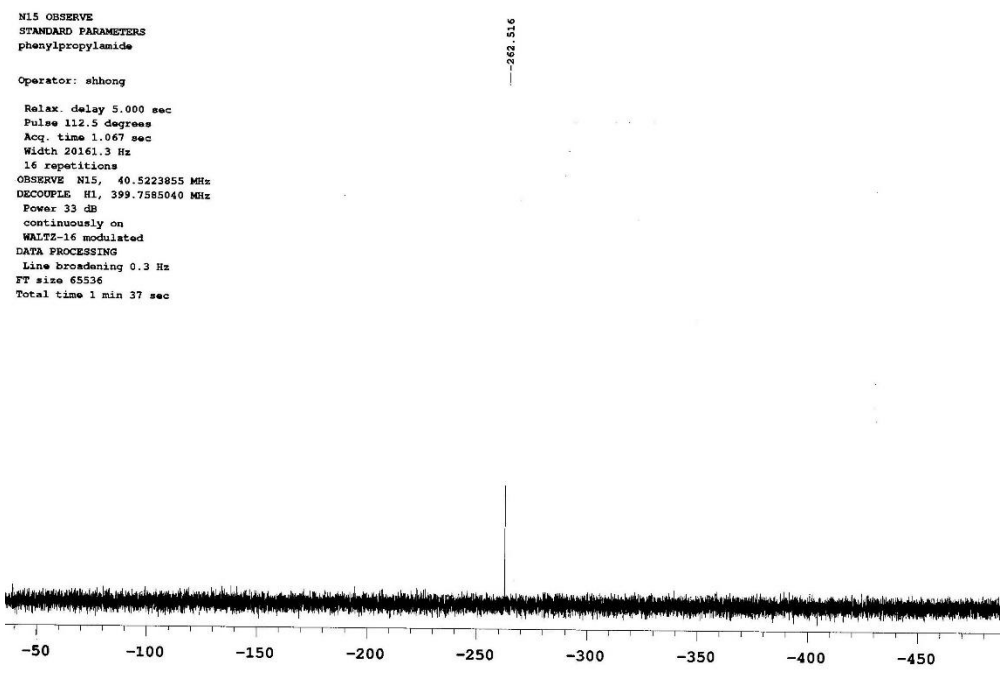




^{13}C NMR (**3aj**) ($CDCl_3$)



^{15}N NMR (**3aj**) ($CDCl_3$)



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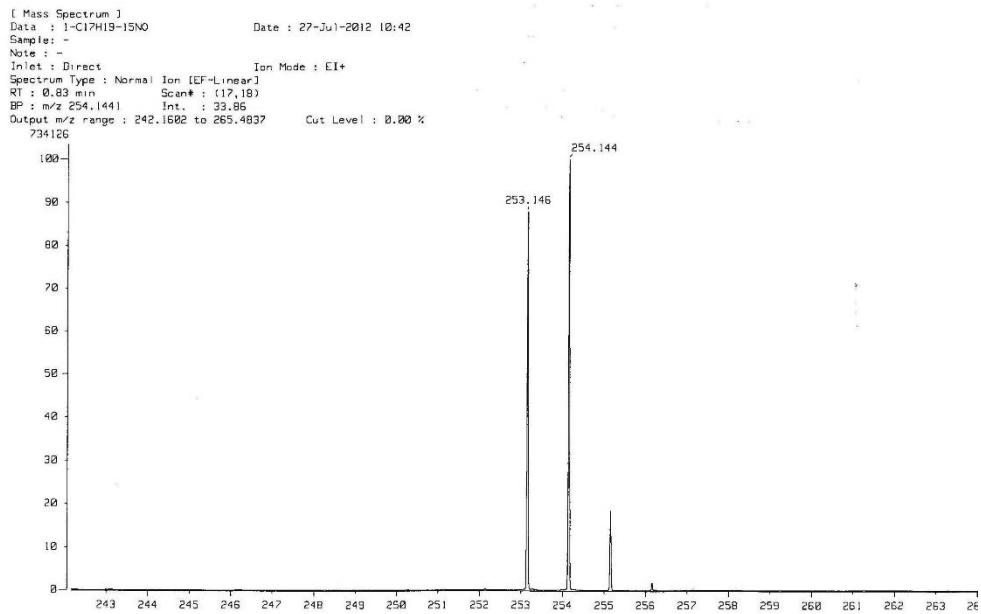
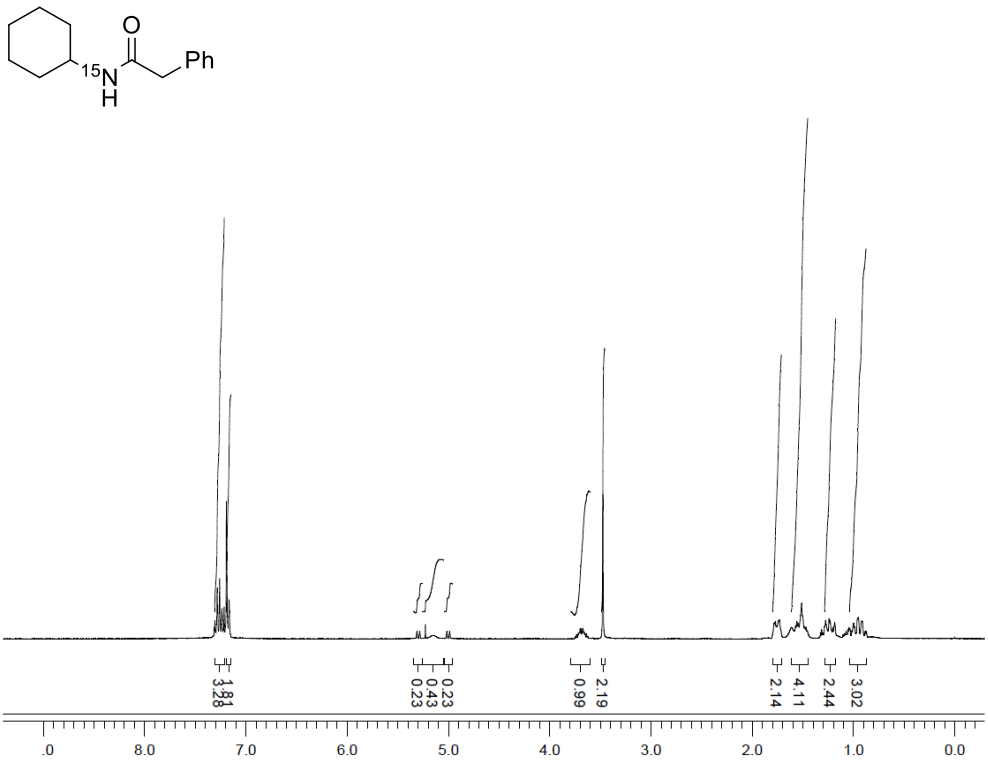
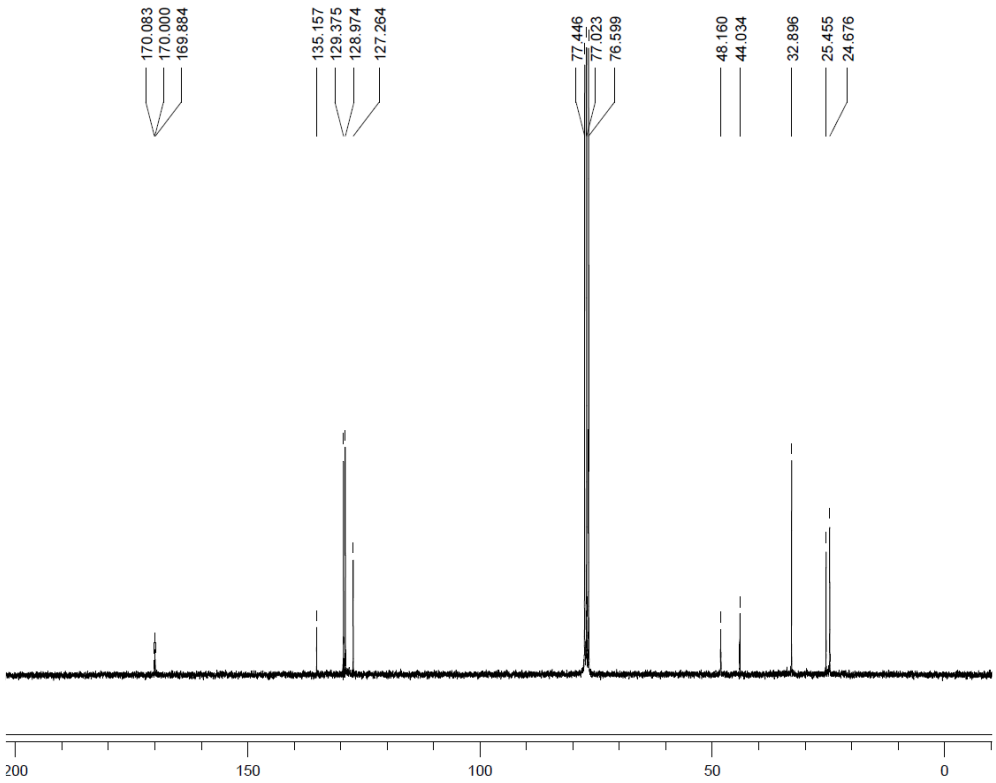


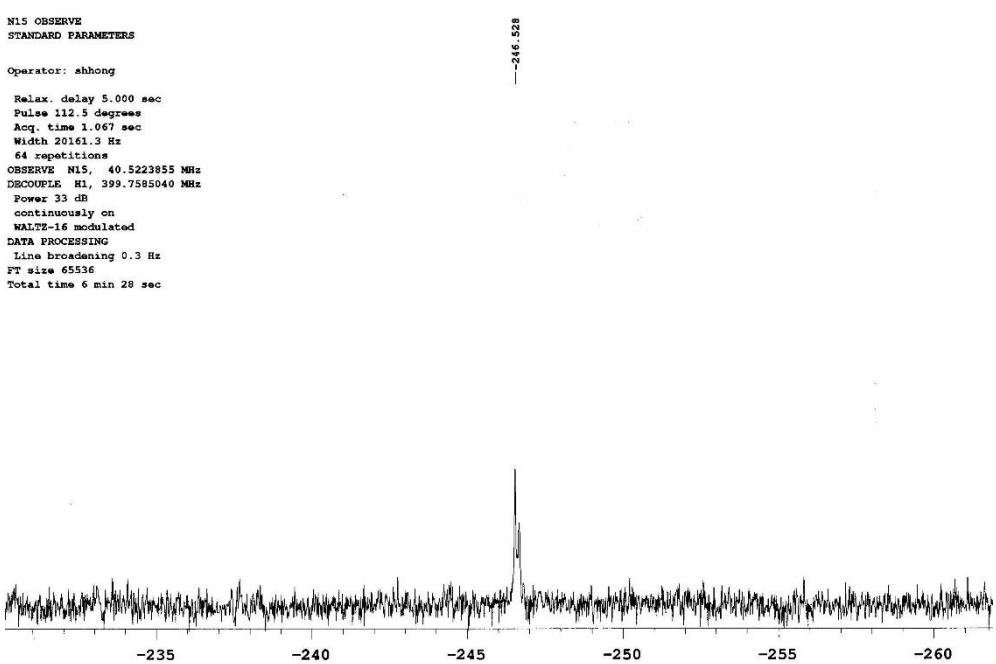
^{1}H NMR (**3ak**) ($CDCl_3$)



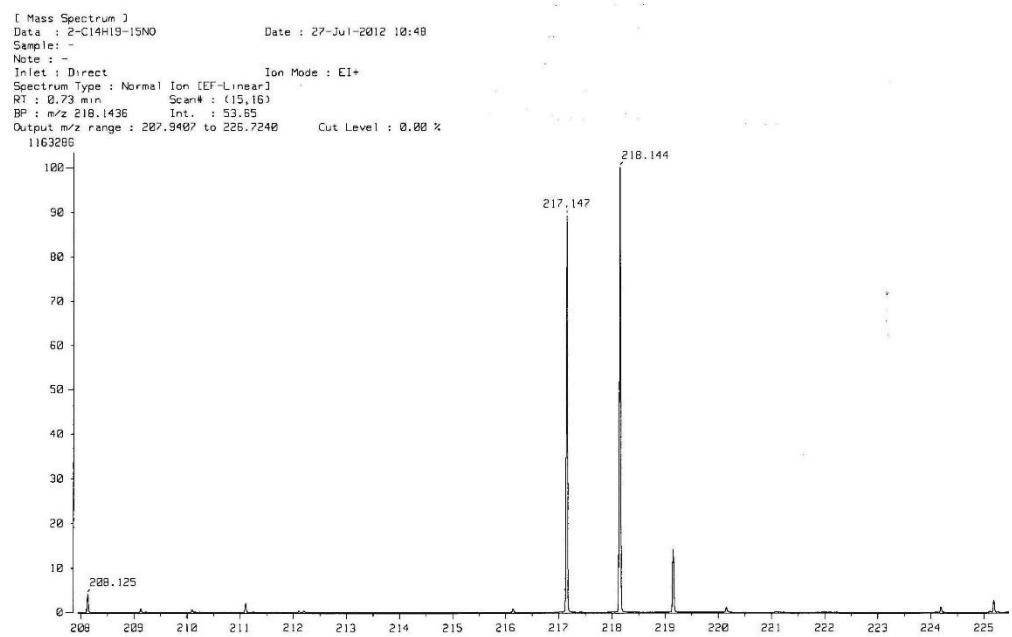
^{13}C NMR (**3ak**) ($CDCl_3$)



^{15}N NMR (**3ak**) ($CDCl_3$)



HR-MS (**3ak**)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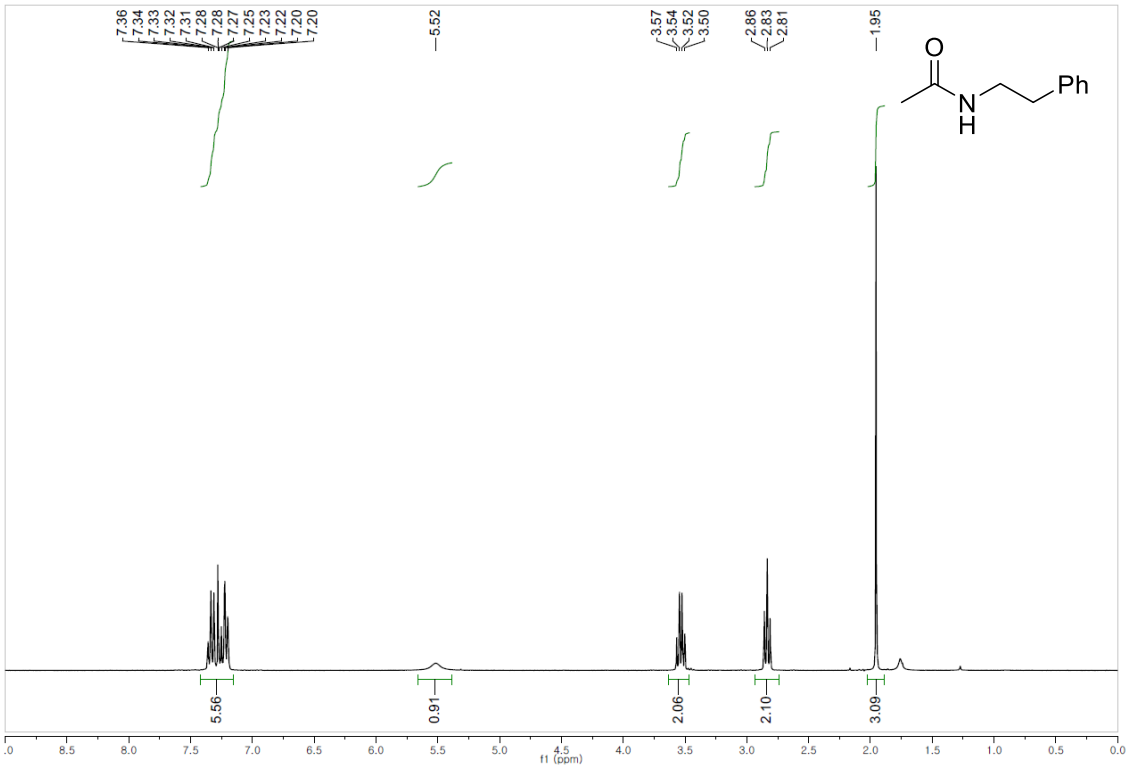
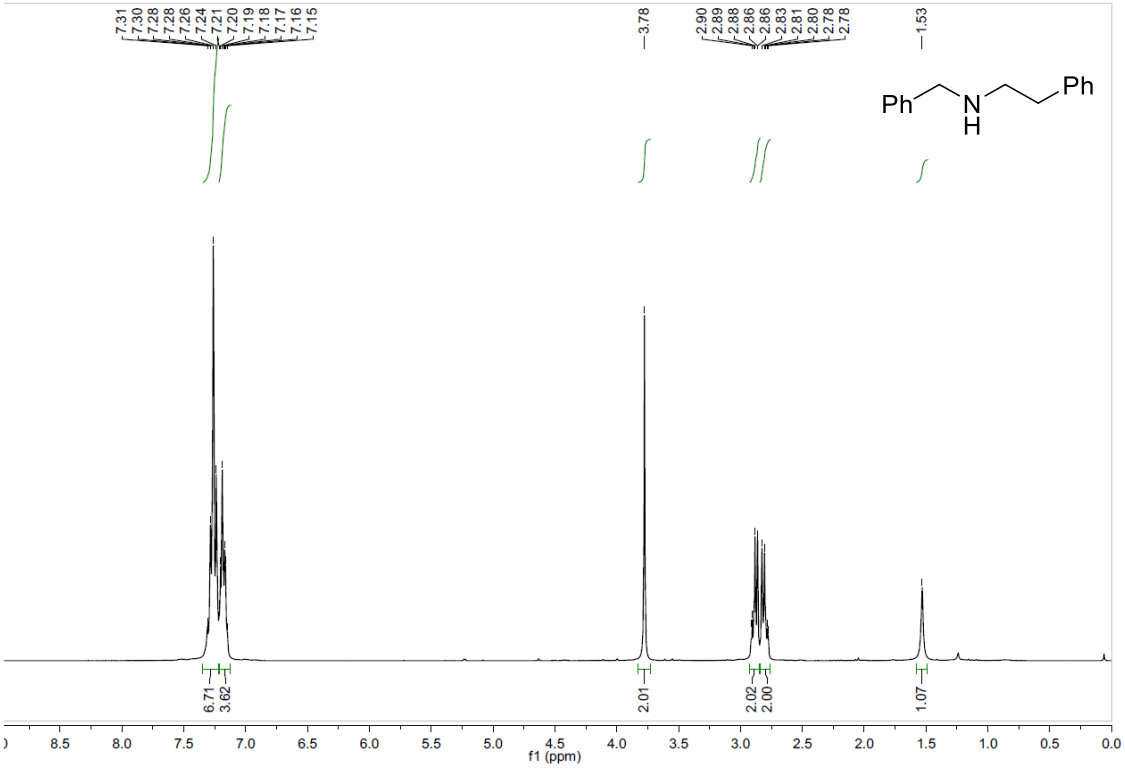
Sample: -
Note : -
Inlet : Direct Ion Mode : EI+
Spectrum Type : Normal Ion [EF-Linear]
RT : 0.73 min Scan# : (15,16)
BP : m/z 218.1436 Int. : 53.85
Output m/z range : 207.9407 to 226.7240 Cut Level : 0.00 %
1163286
218.144
217.147
208.125

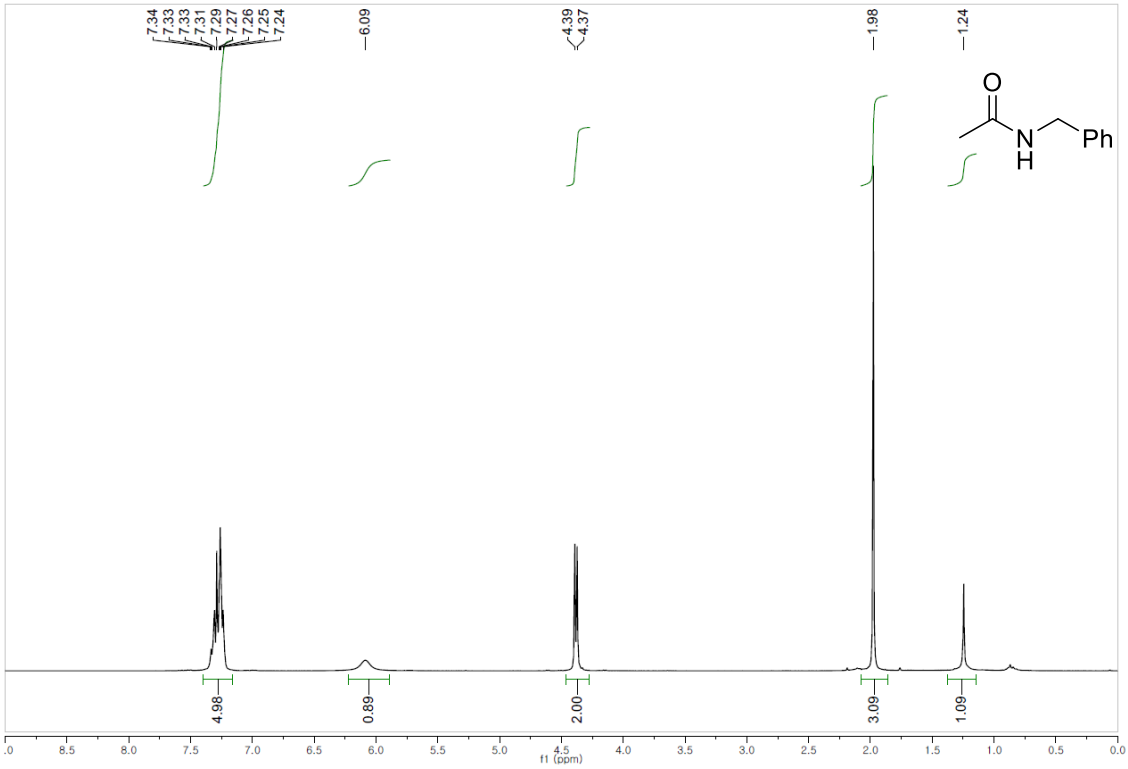
^{1}H NMR (**3a**) ($CDCl_3$)



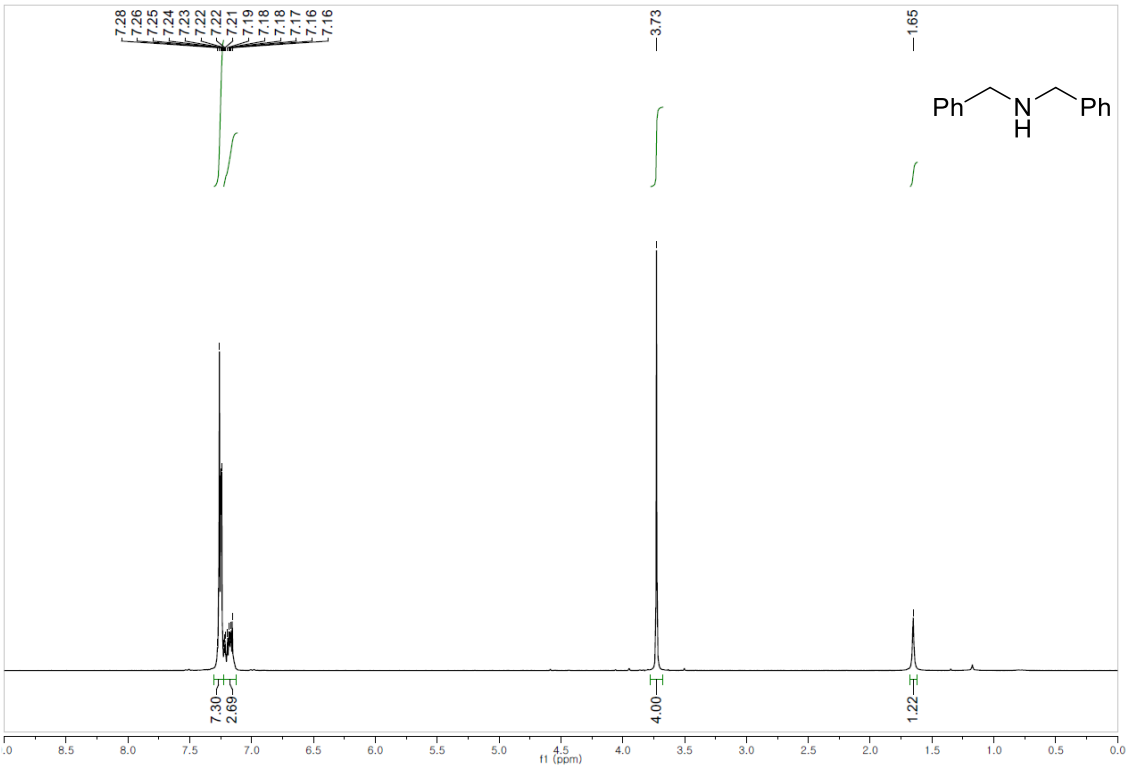
^{1}H NMR (**4a**) ($CDCl_3$)



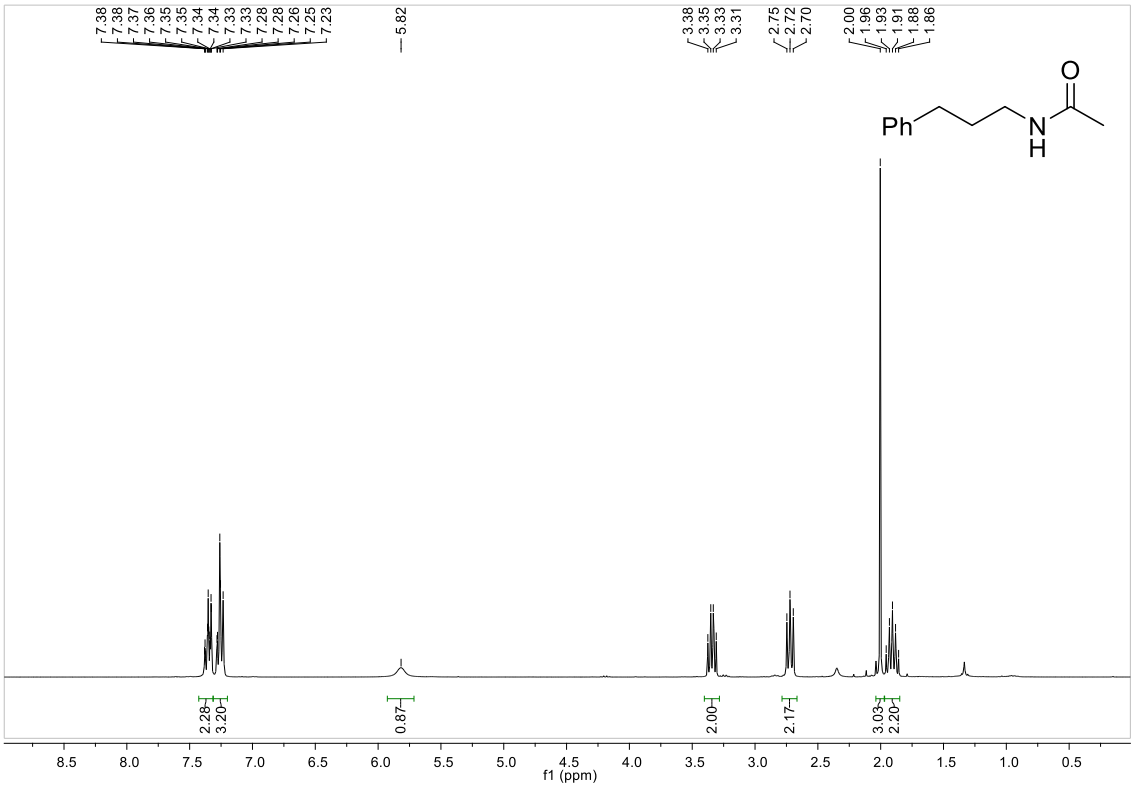
^{1}H NMR (**3b**) ($CDCl_3$)



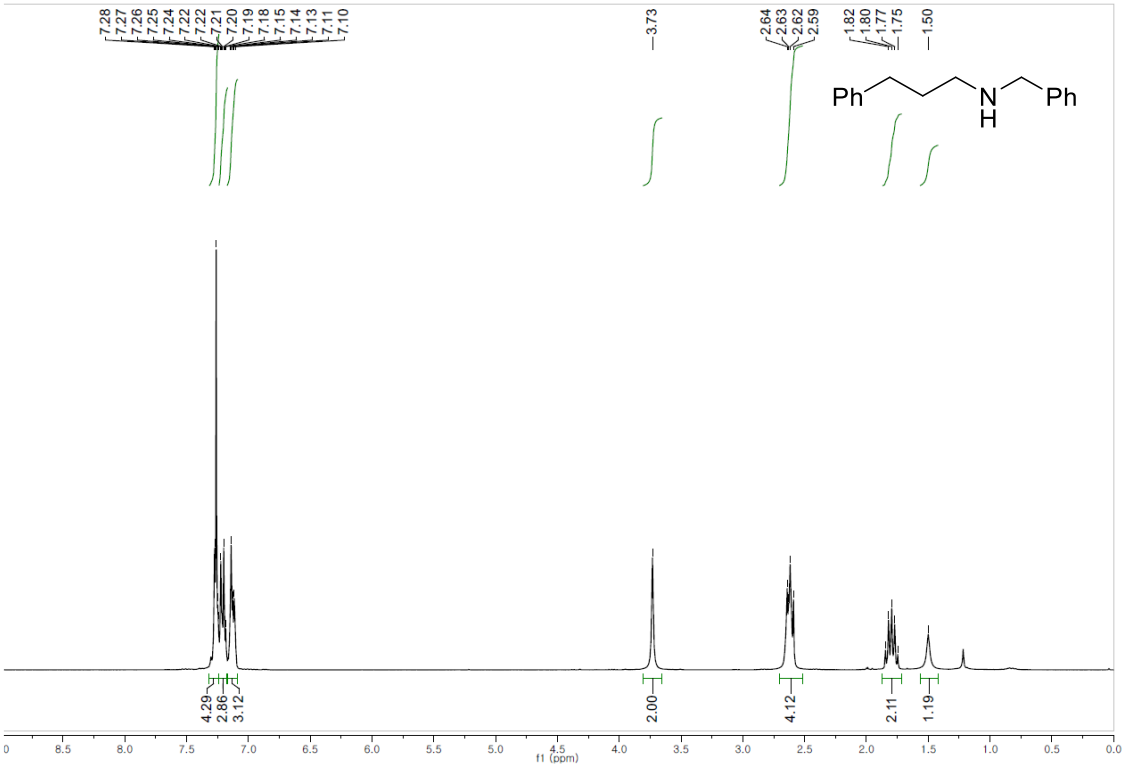
^{1}H NMR (**4b**) ($CDCl_3$)



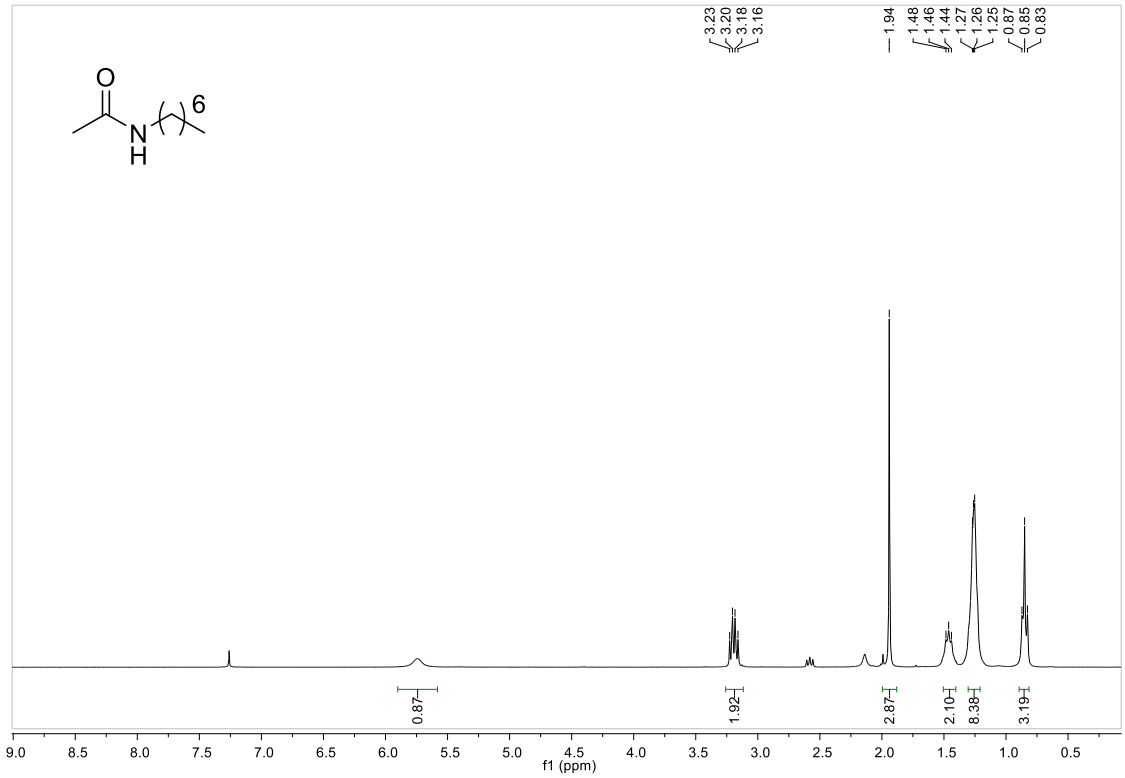
^{1}H NMR (**3c**) ($CDCl_3$)



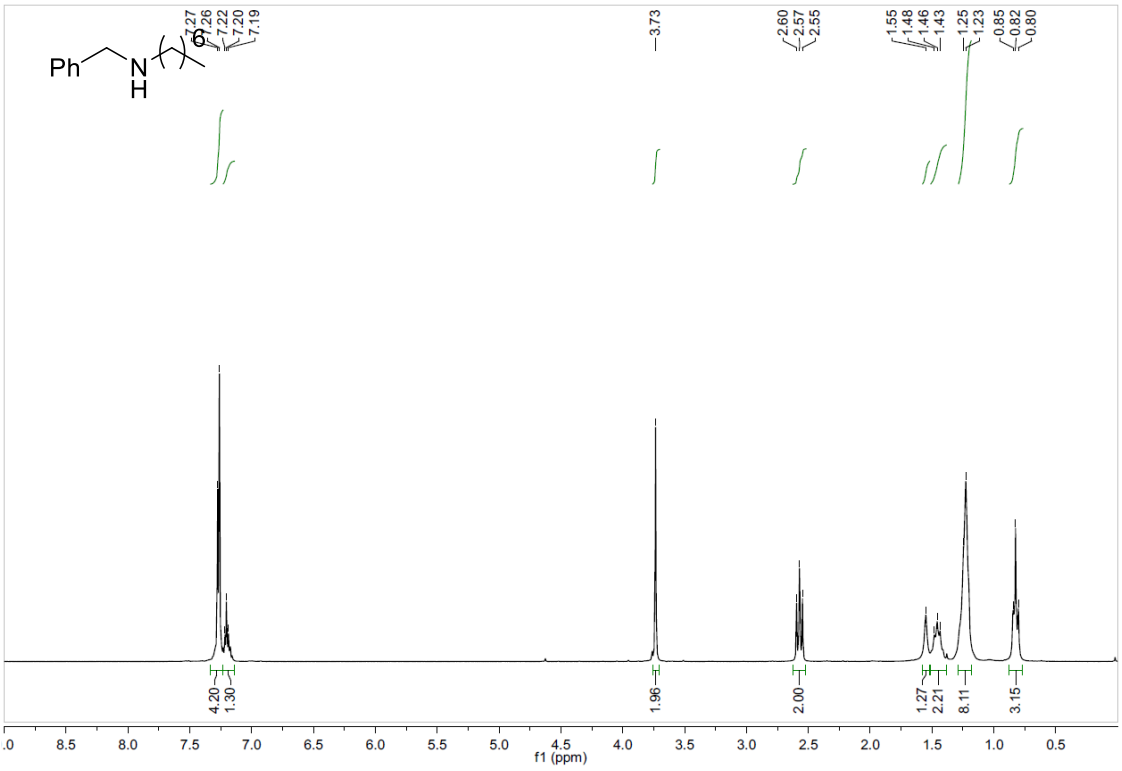
^{1}H NMR (**4c**) ($CDCl_3$)



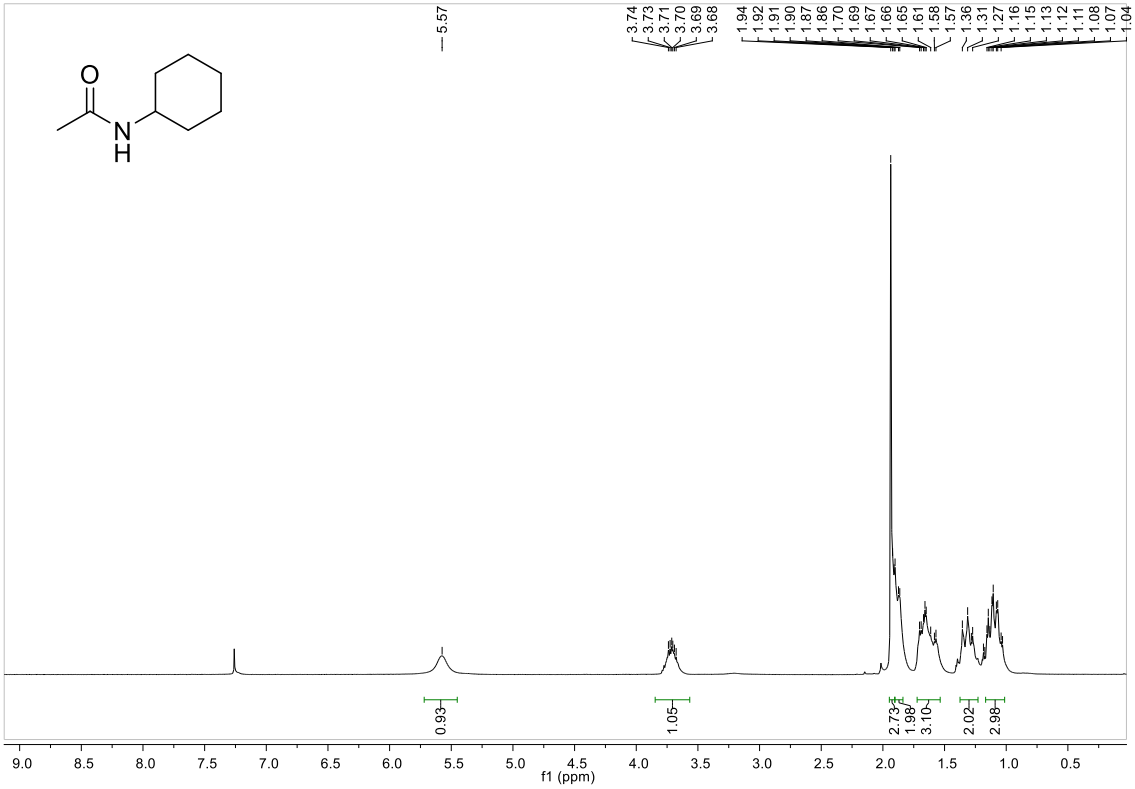
^{1}H NMR (**3d**) ($CDCl_3$)



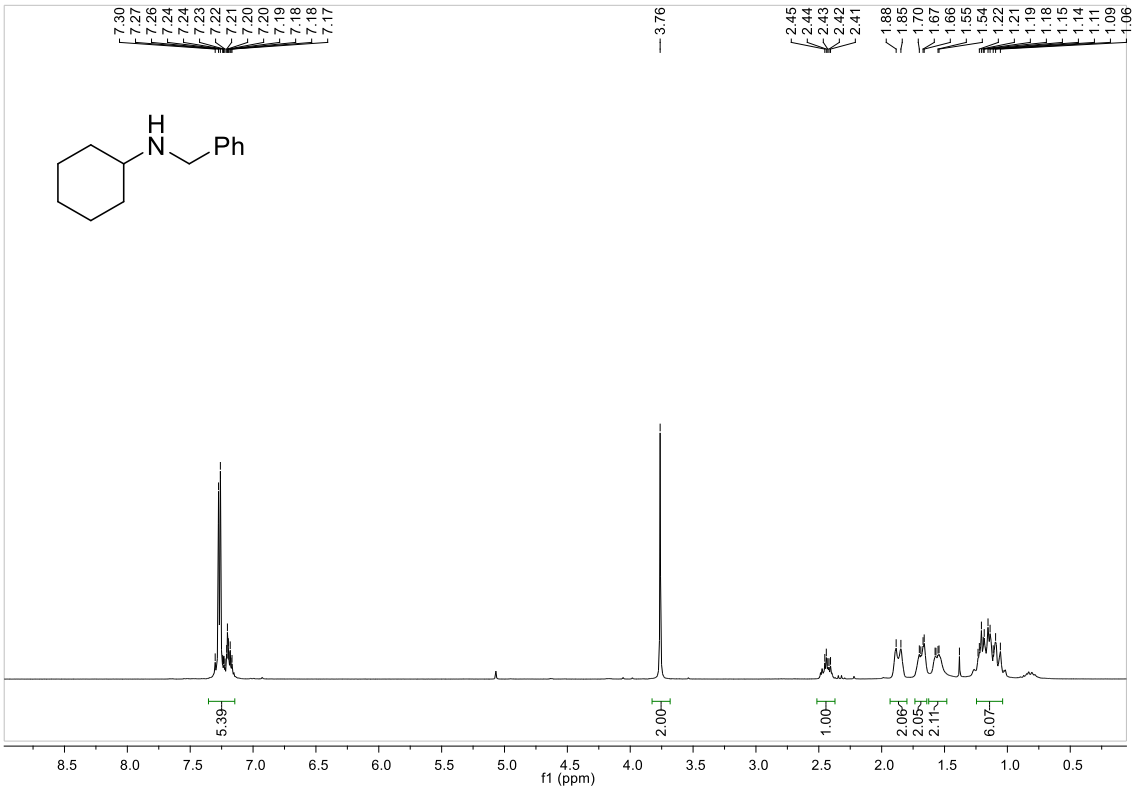
^{1}H NMR (**4d**) ($CDCl_3$)



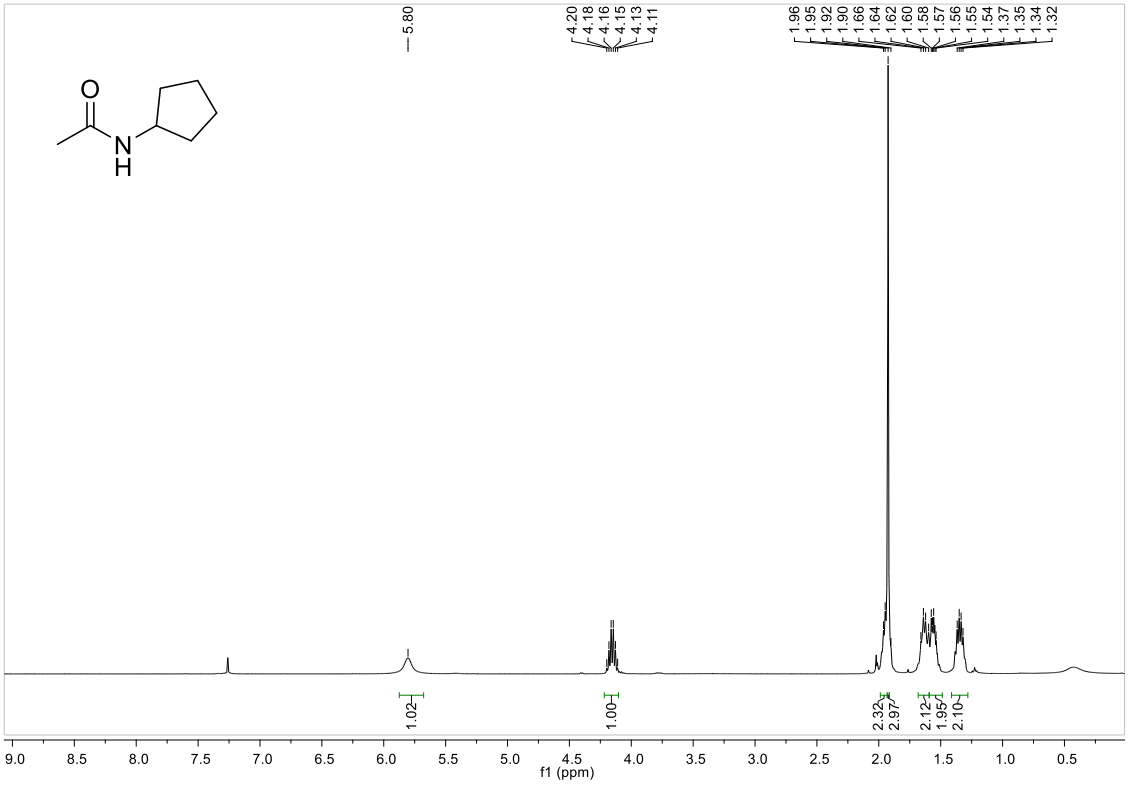
^{1}H NMR (**3e**) ($CDCl_3$)



^{1}H NMR (**4e**) ($CDCl_3$)



^{1}H NMR (**3f**) ($CDCl_3$)



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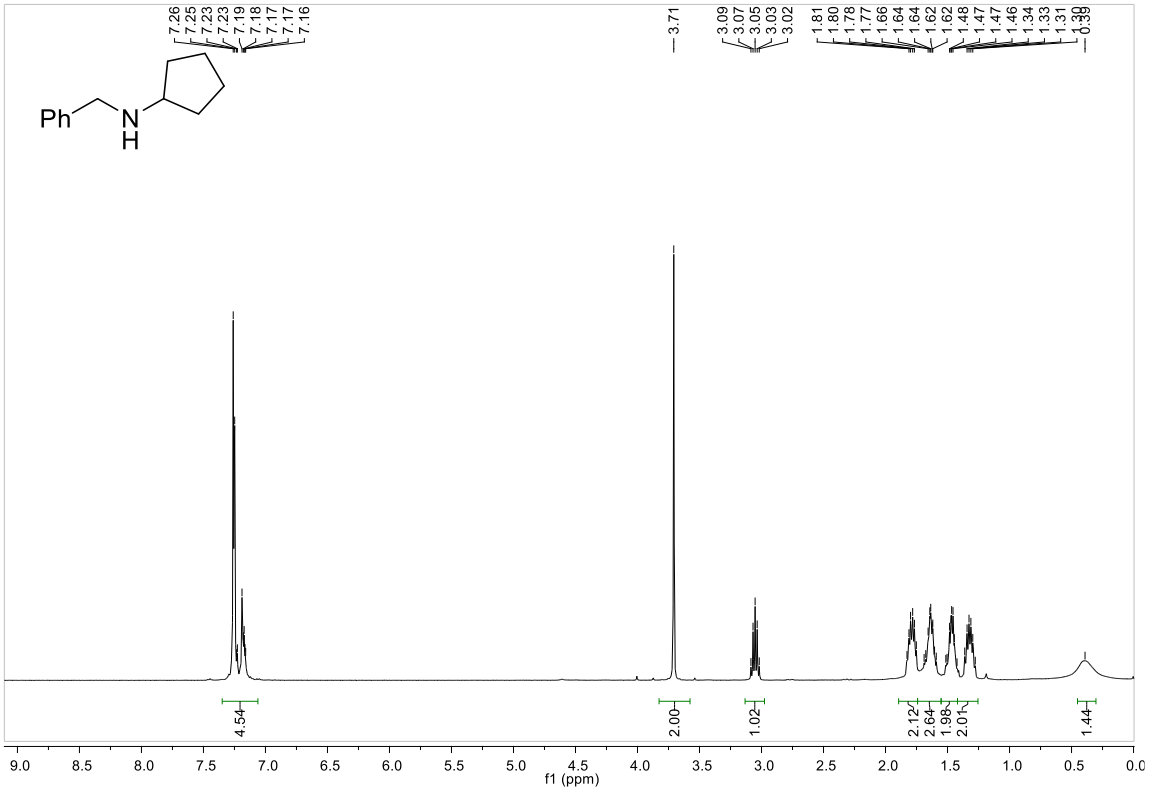
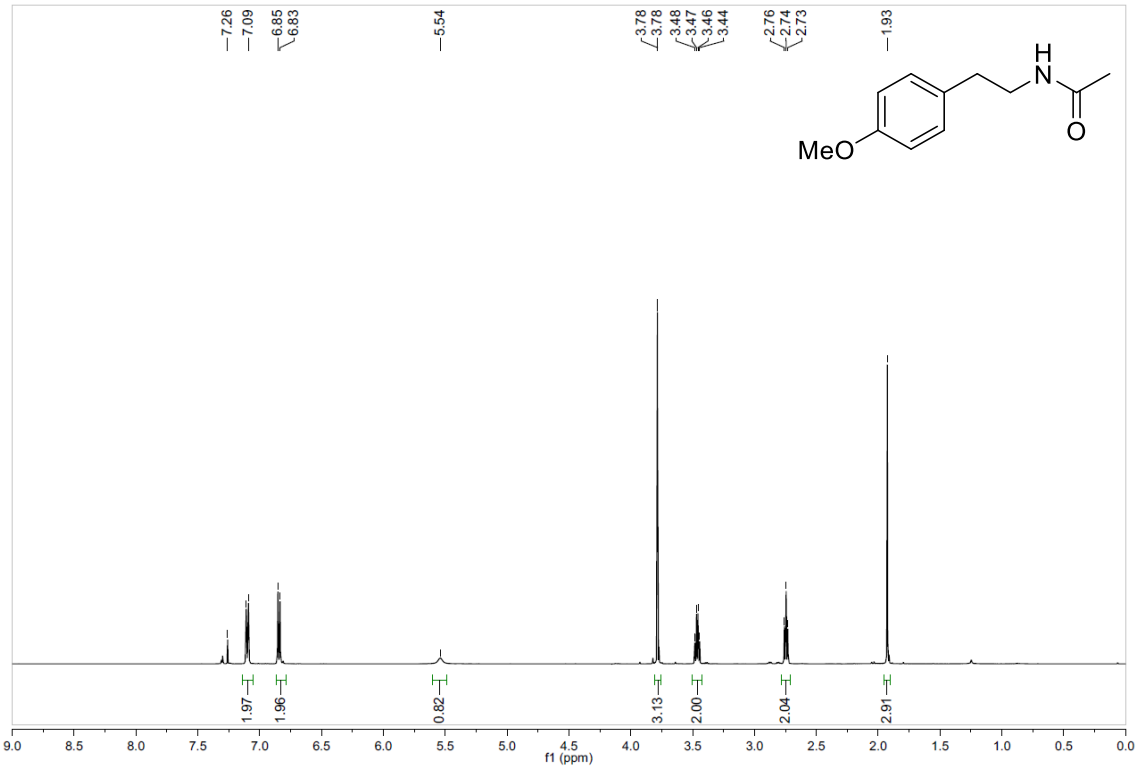


^{1}H NMR (**3g**) ($CDCl_3$)



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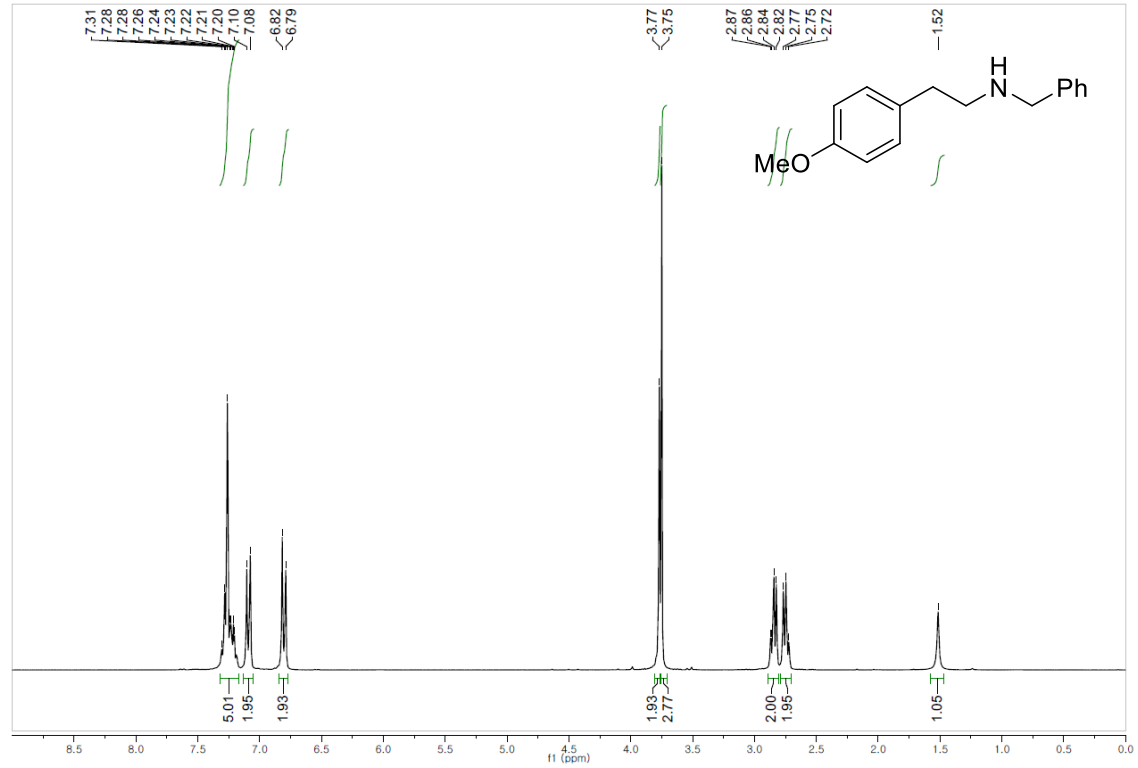

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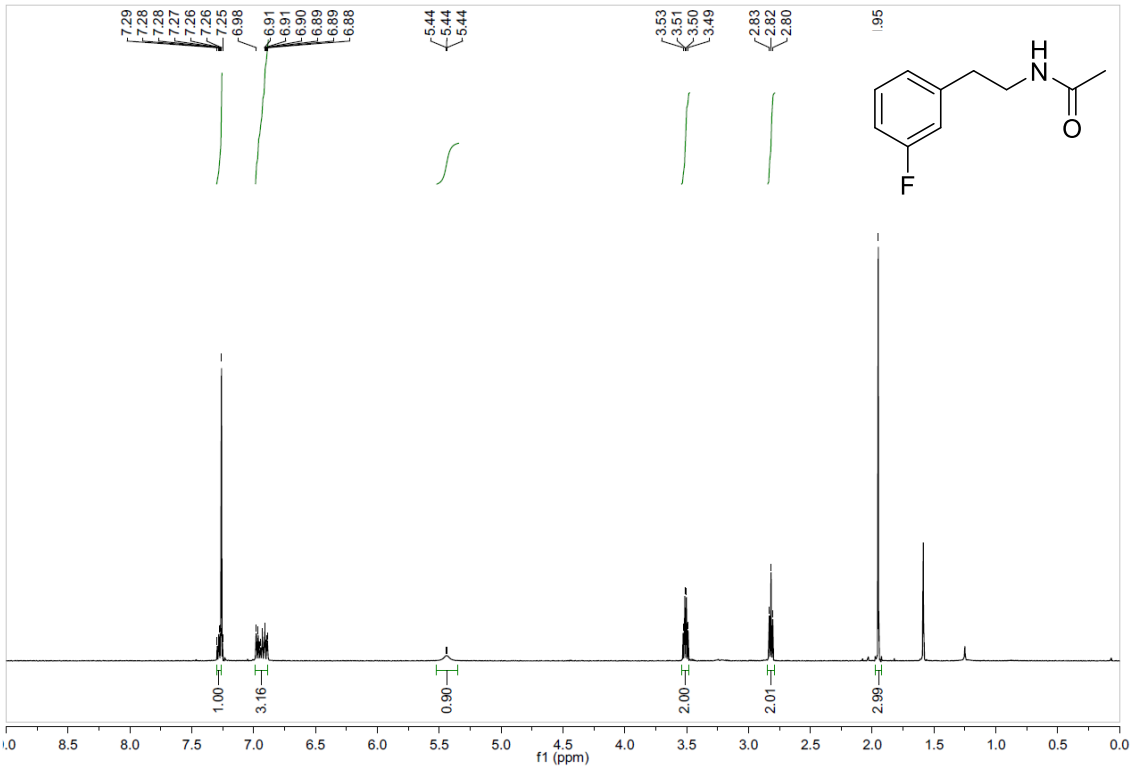

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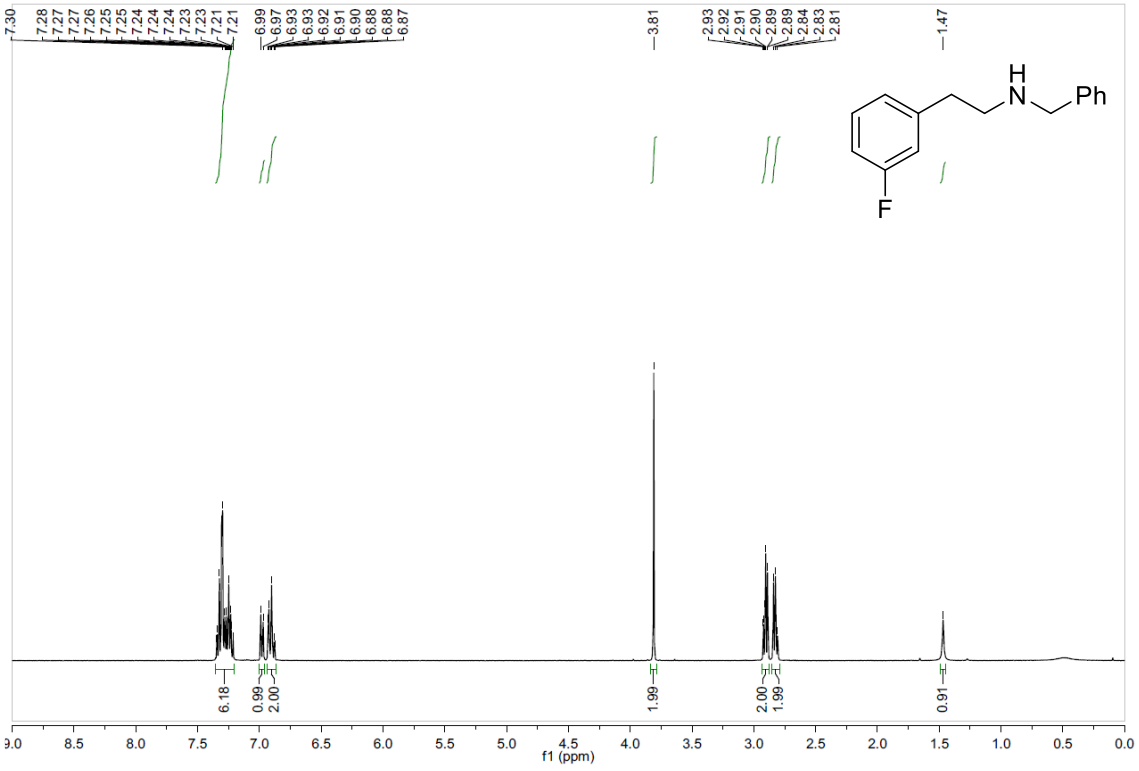
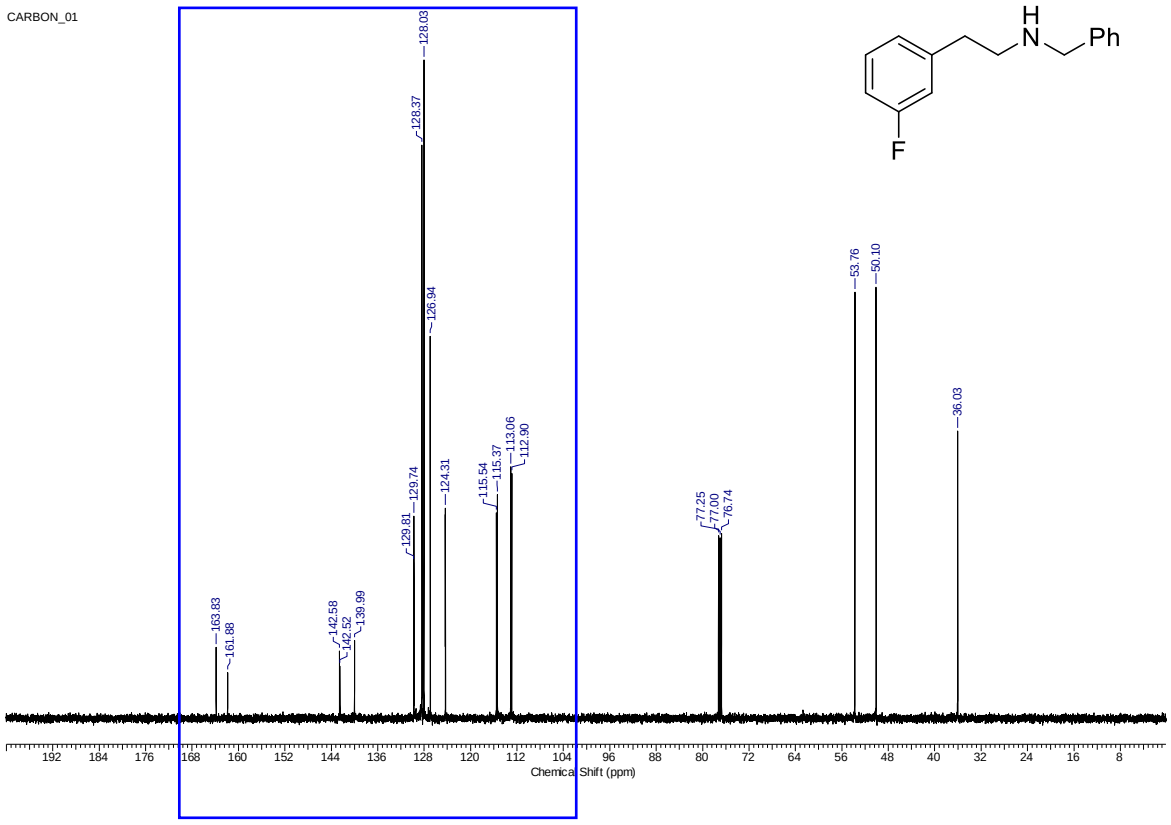
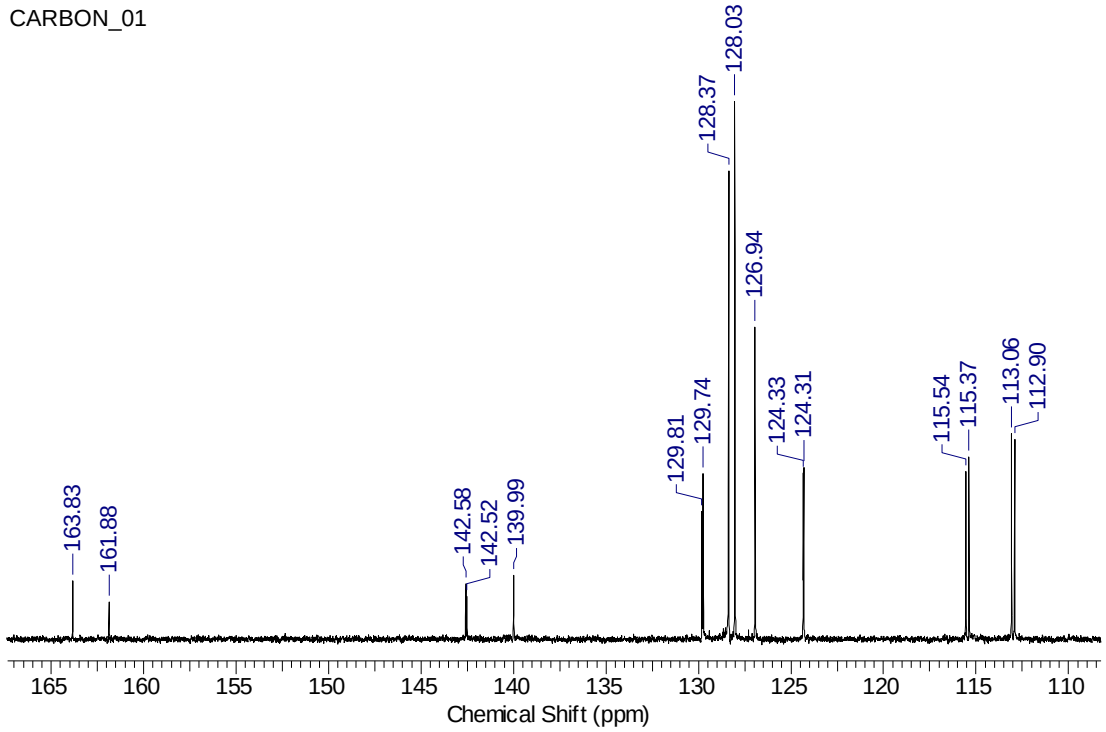
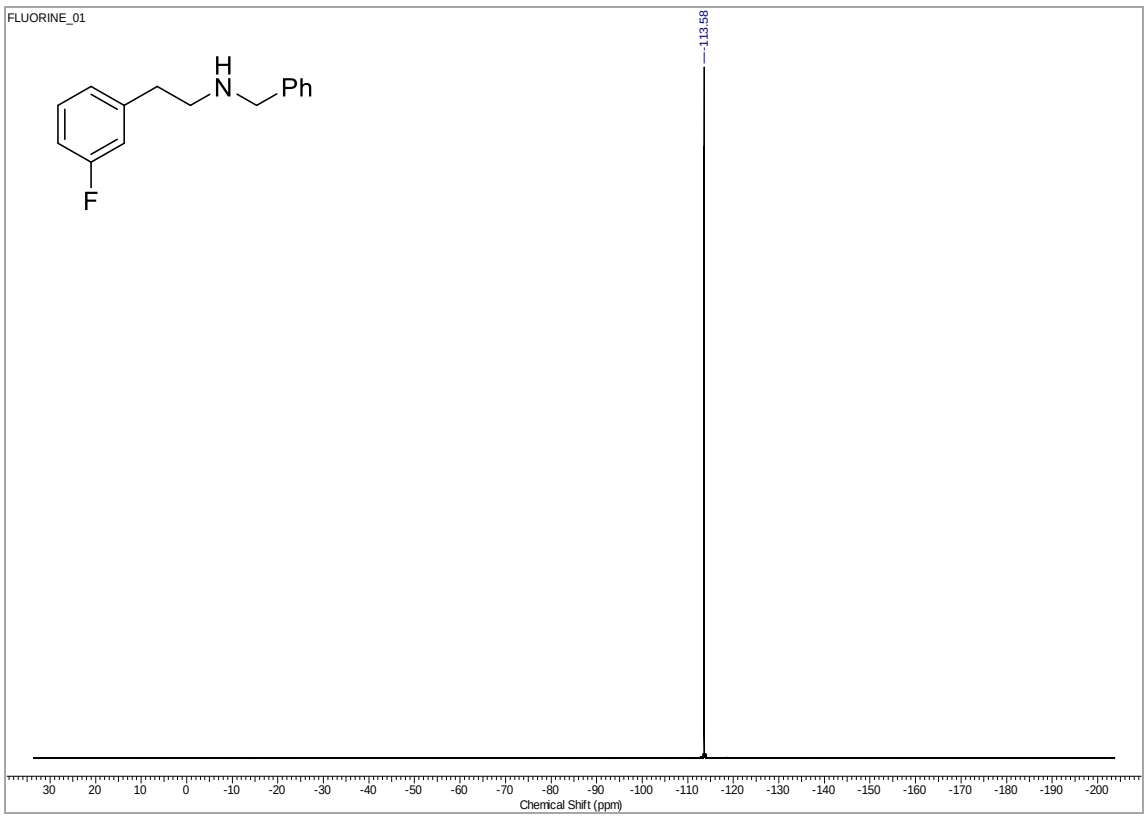


^{13}C NMR (**4h**) ($CDCl_3$)

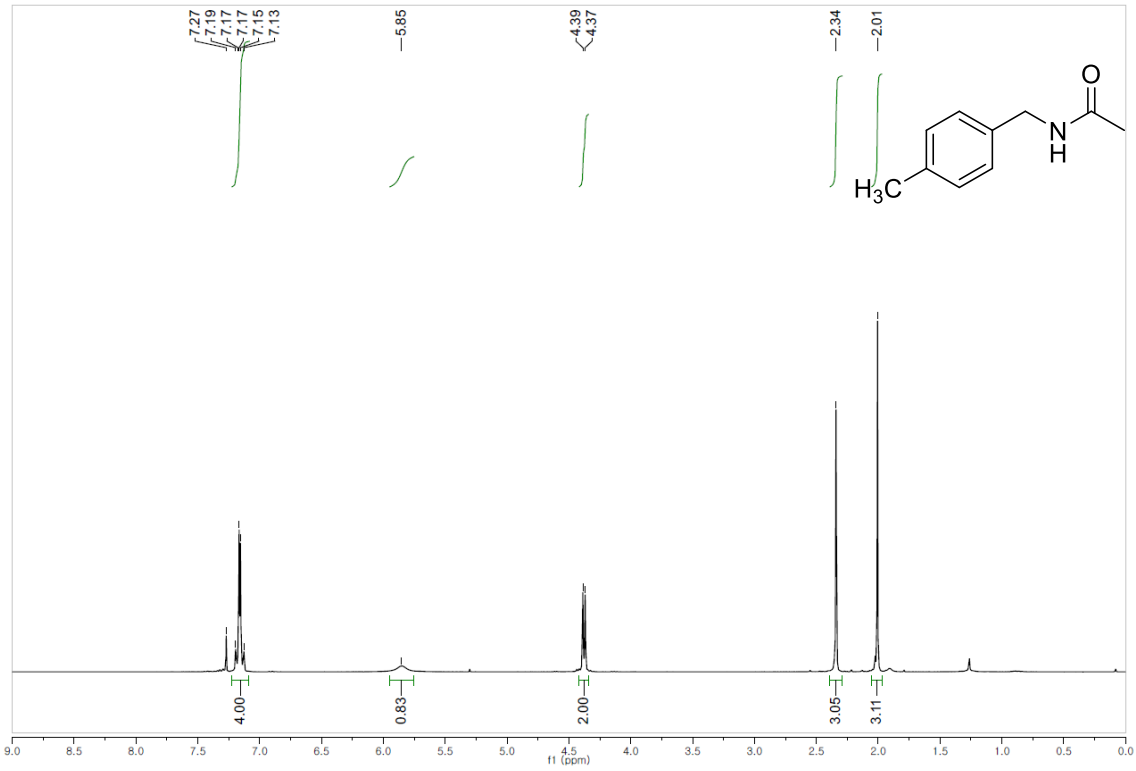




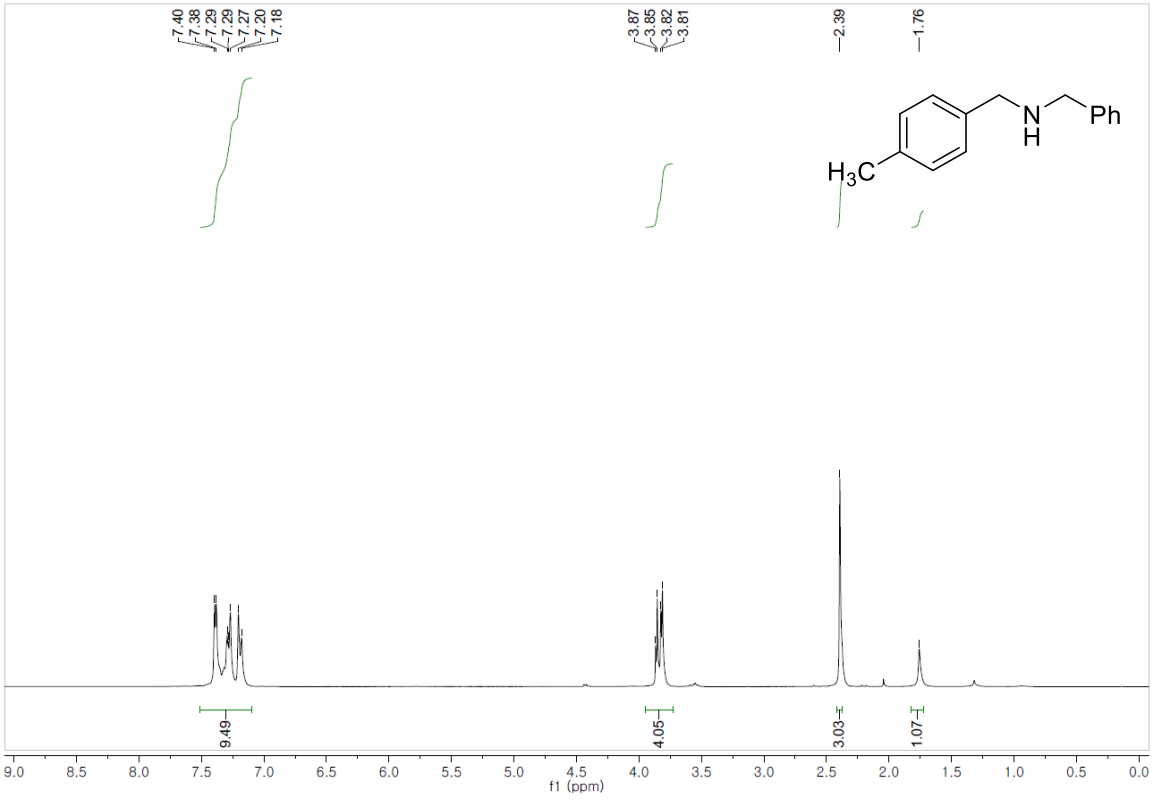
^{19}F NMR (**4h**) ($CDCl_3$



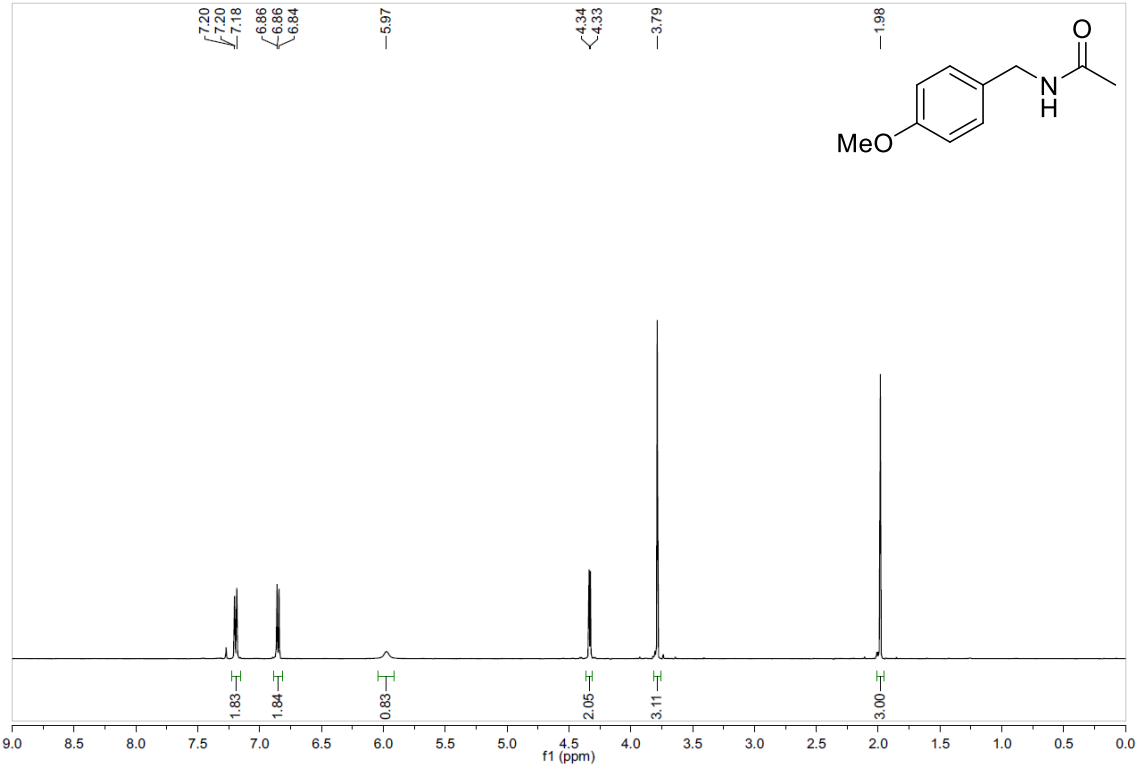
^{1}H NMR (**3i**) ($CDCl_3$)



^{1}H NMR (**4i**) ($CDCl_3$)



^{1}H NMR (**3j**) ($CDCl_3$)



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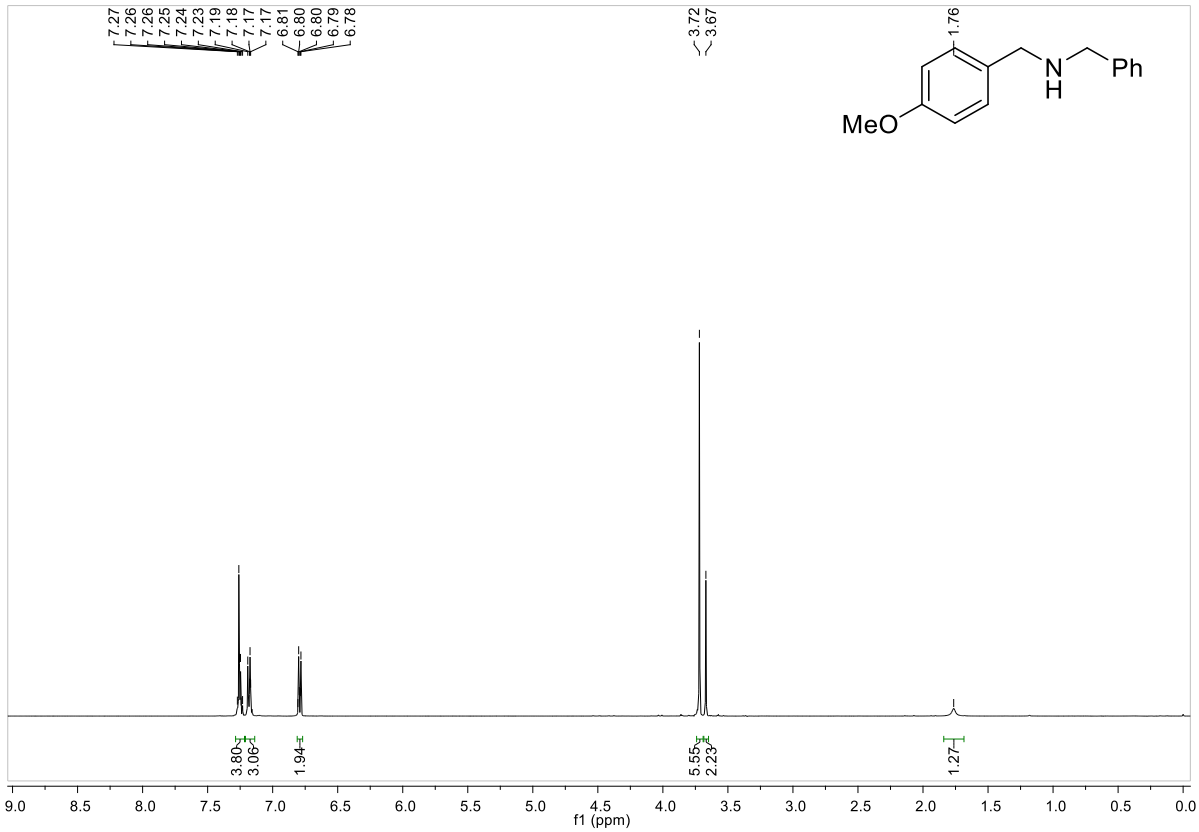
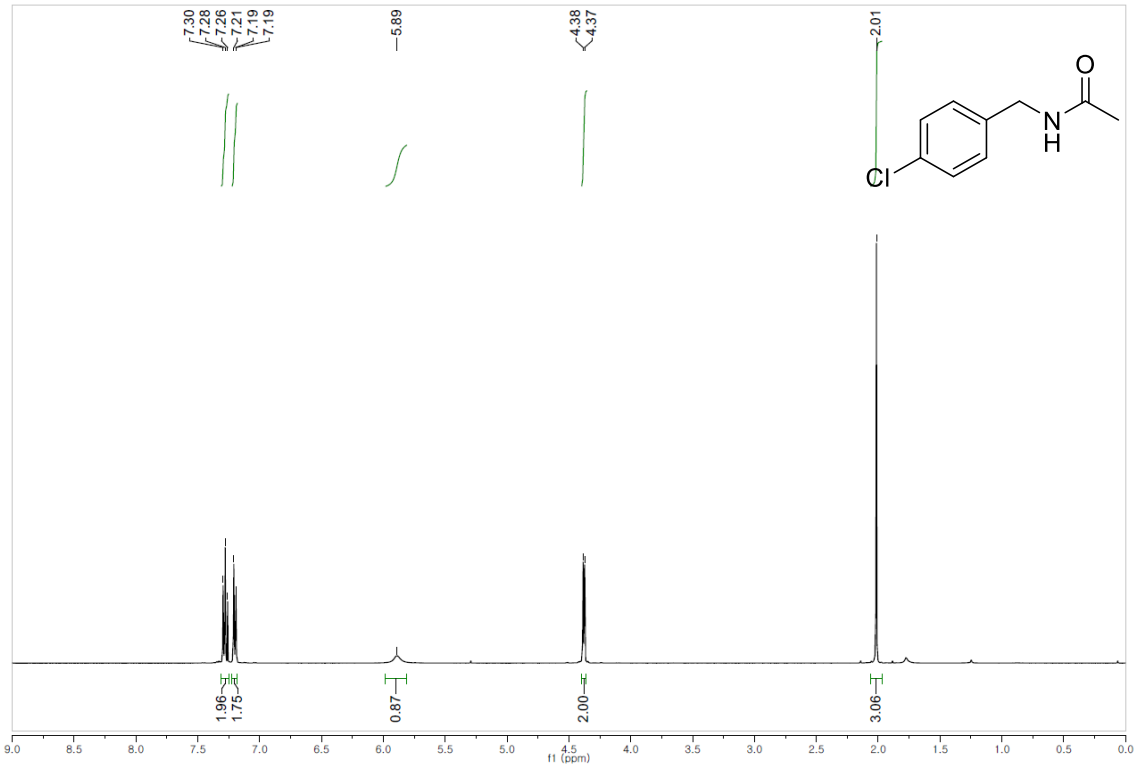
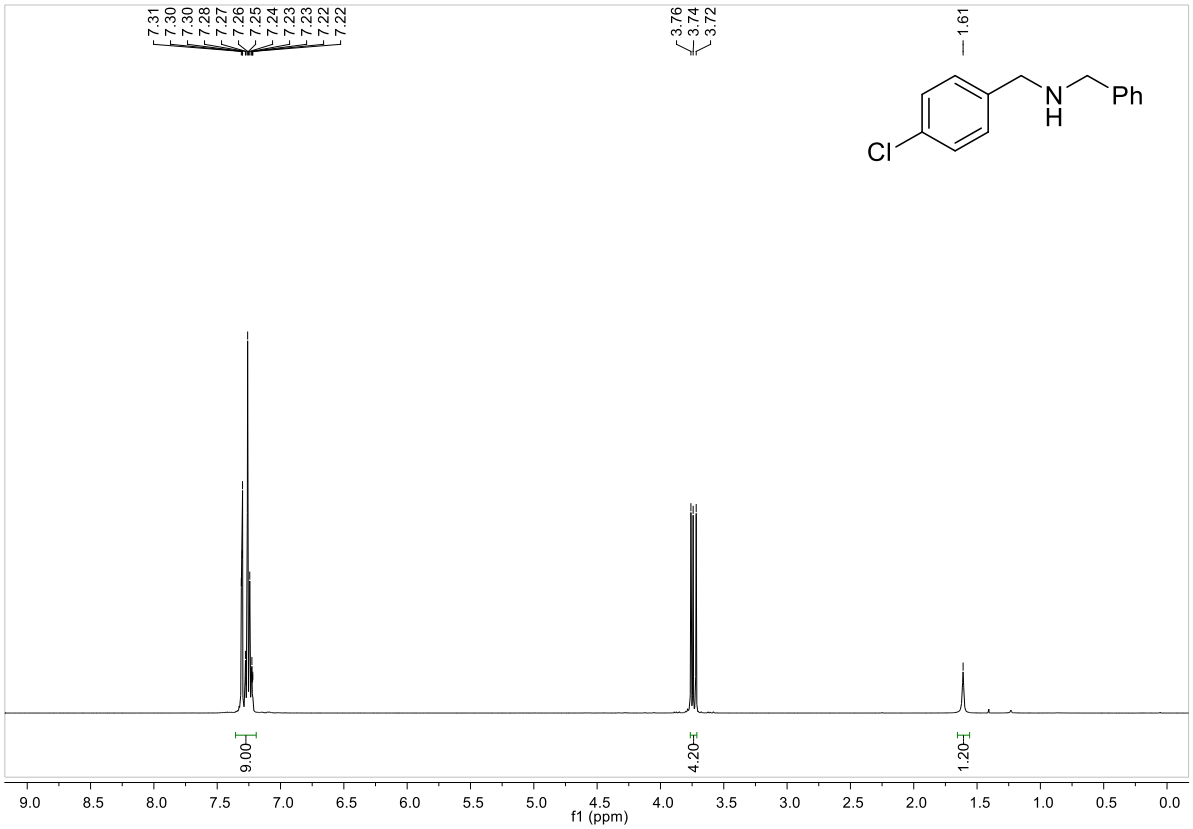


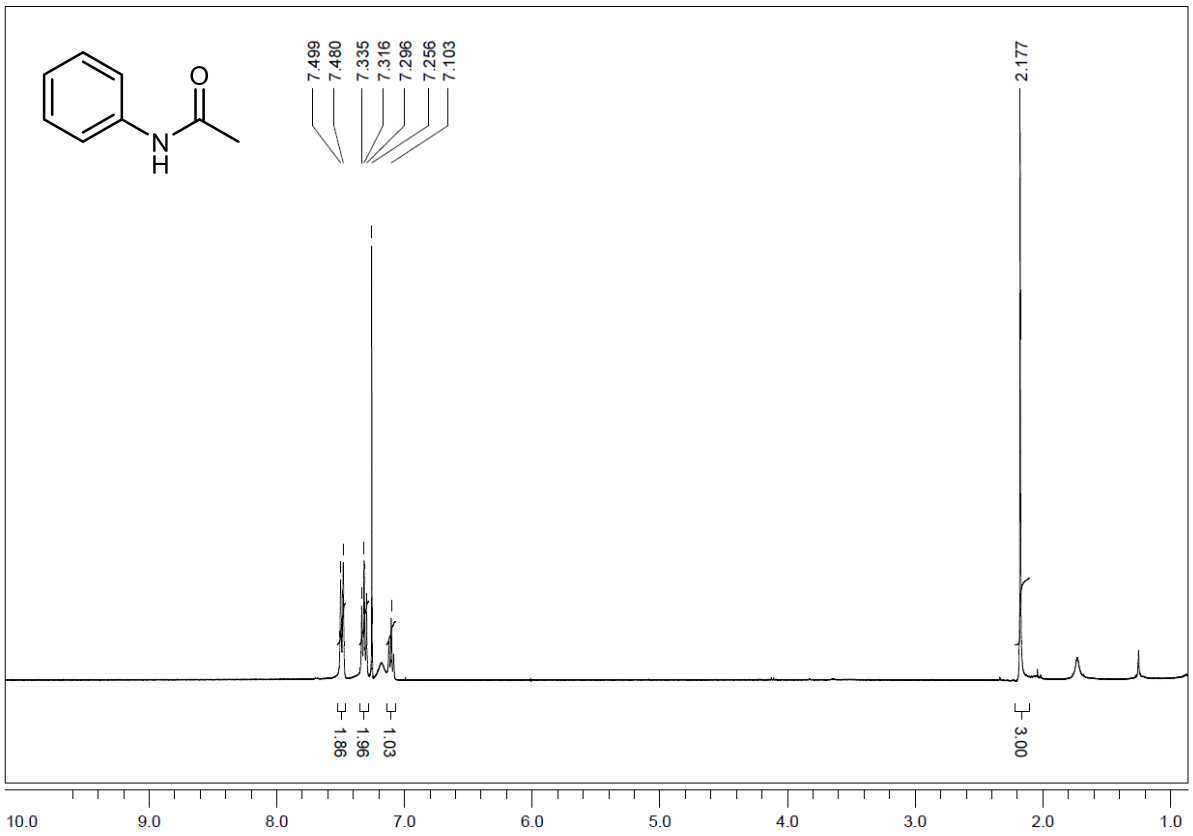
^{1}H NMR (**3k**) ($CDCl_3$)



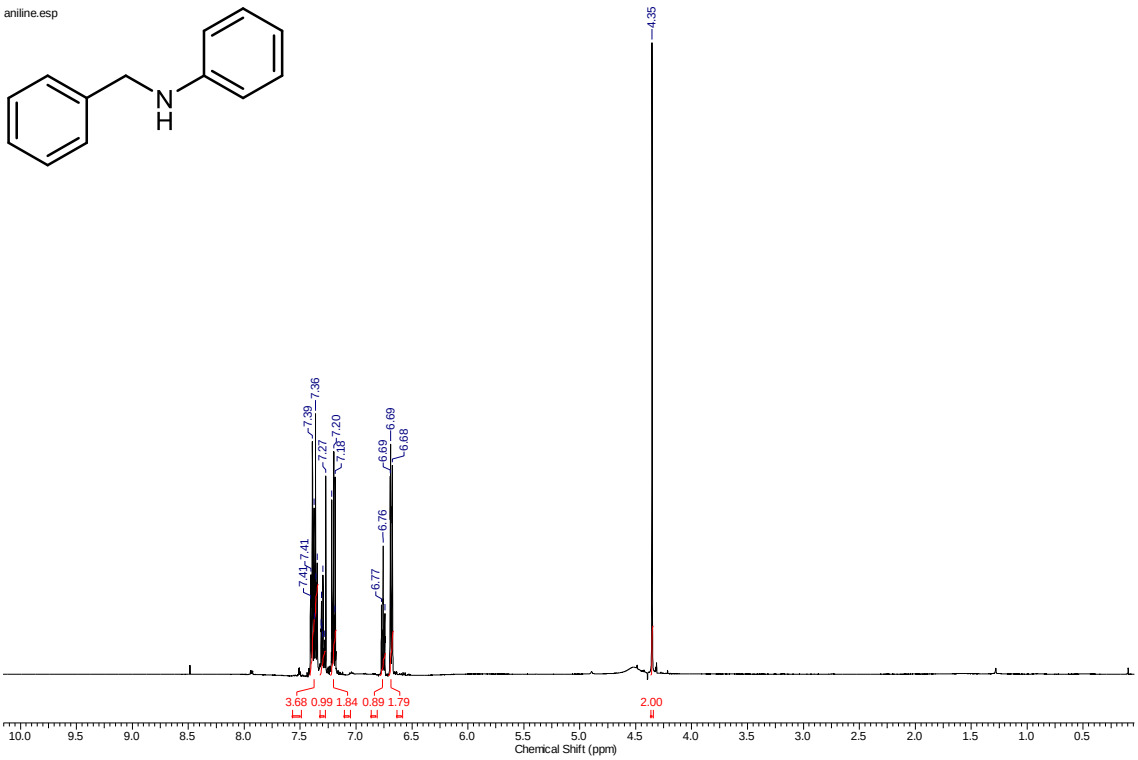
^{1}H NMR (**4k**) ($CDCl_3$)



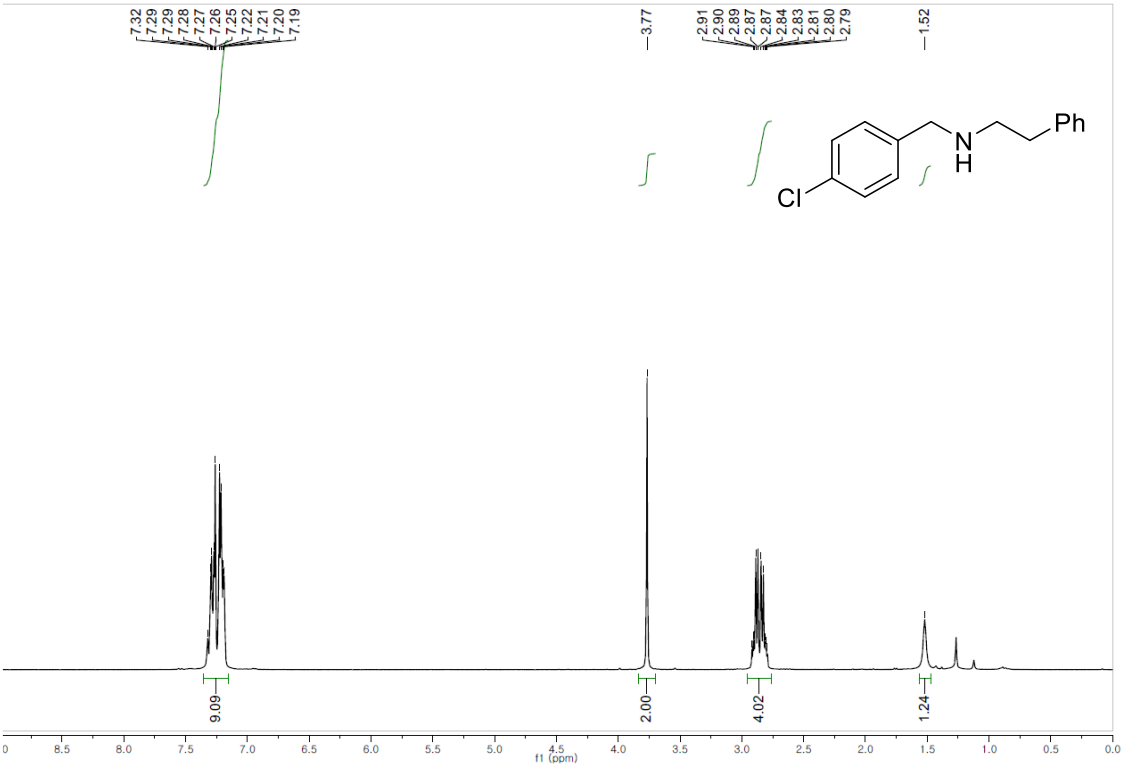
^{1}H NMR (**3l**) ($CDCl_3$)



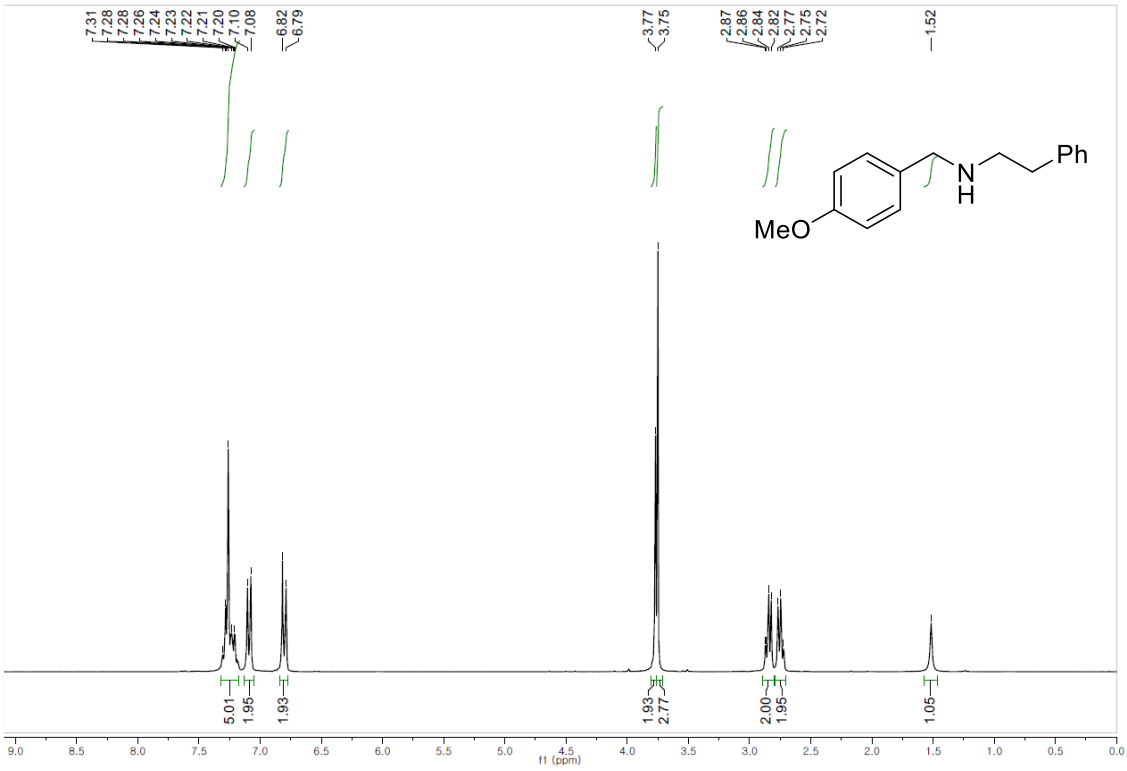
^{1}H NMR (**4l**) ($CDCl_3$)



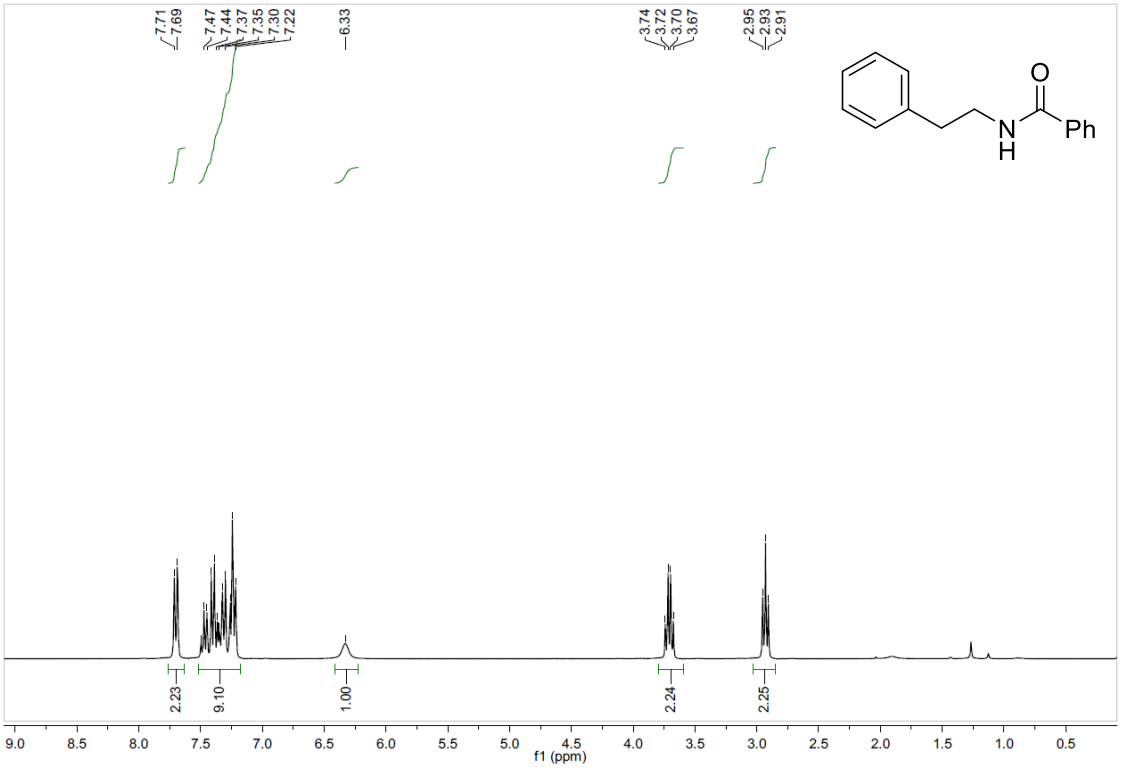
^{1}H NMR (**6b**) ($CDCl_3$)



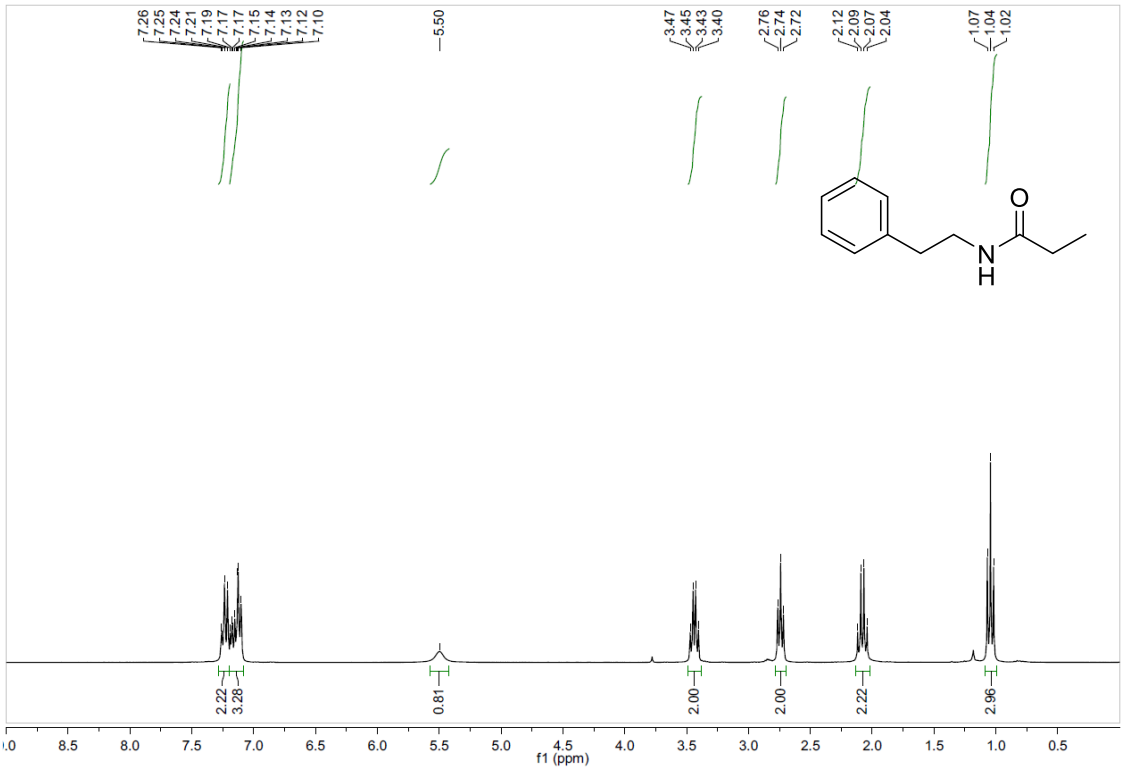
^{1}H NMR (**6c**) ($CDCl_3$)



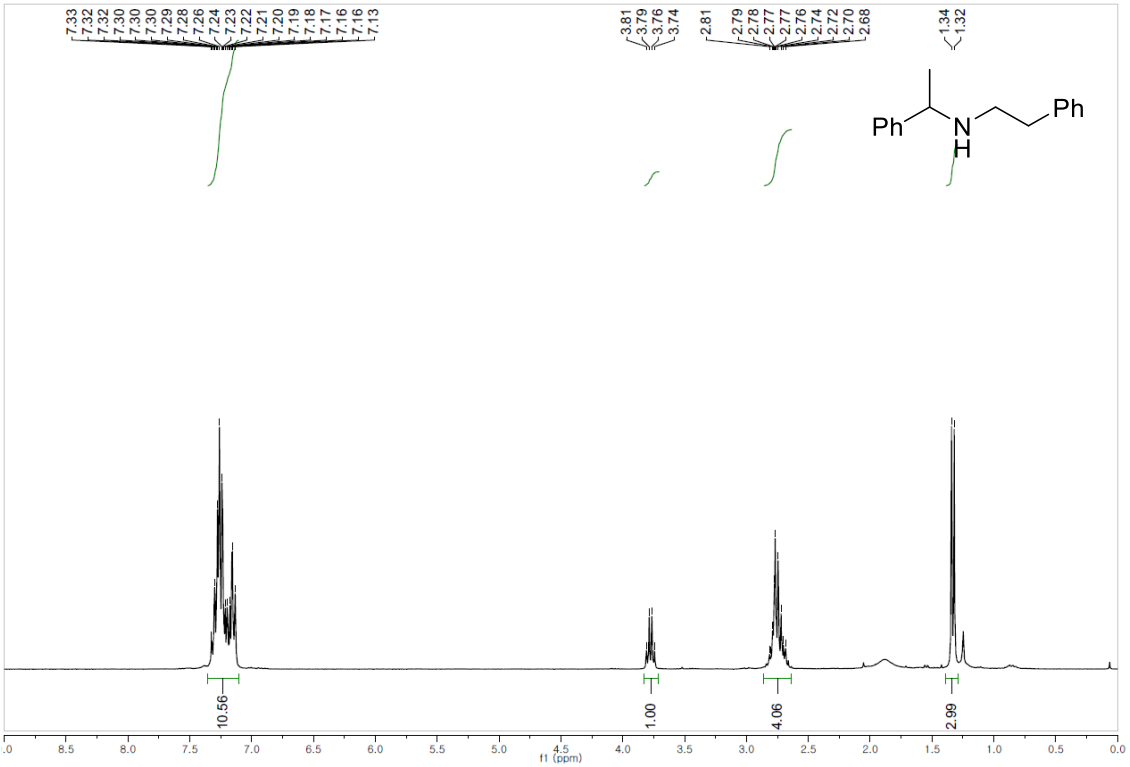
^{1}H NMR (**5d**) ($CDCl_3$)



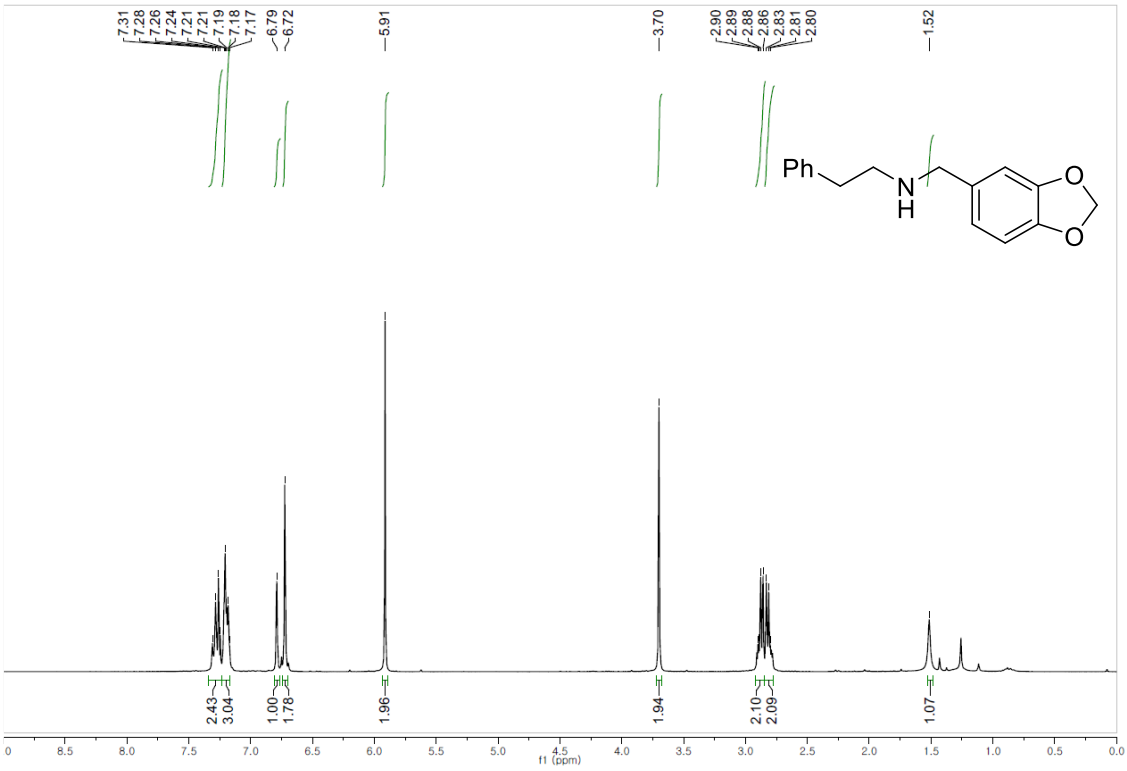
^{1}H NMR (**5e**) ($CDCl_3$)



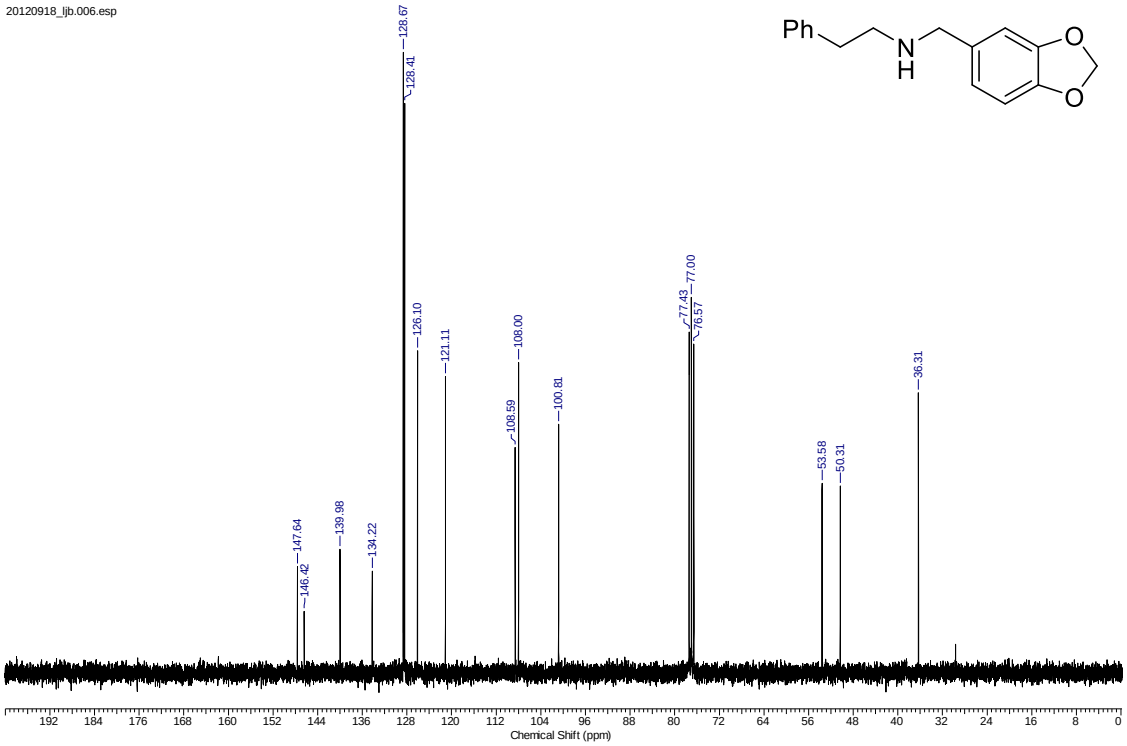
^{1}H NMR (**5f**) ($CDCl_3$)



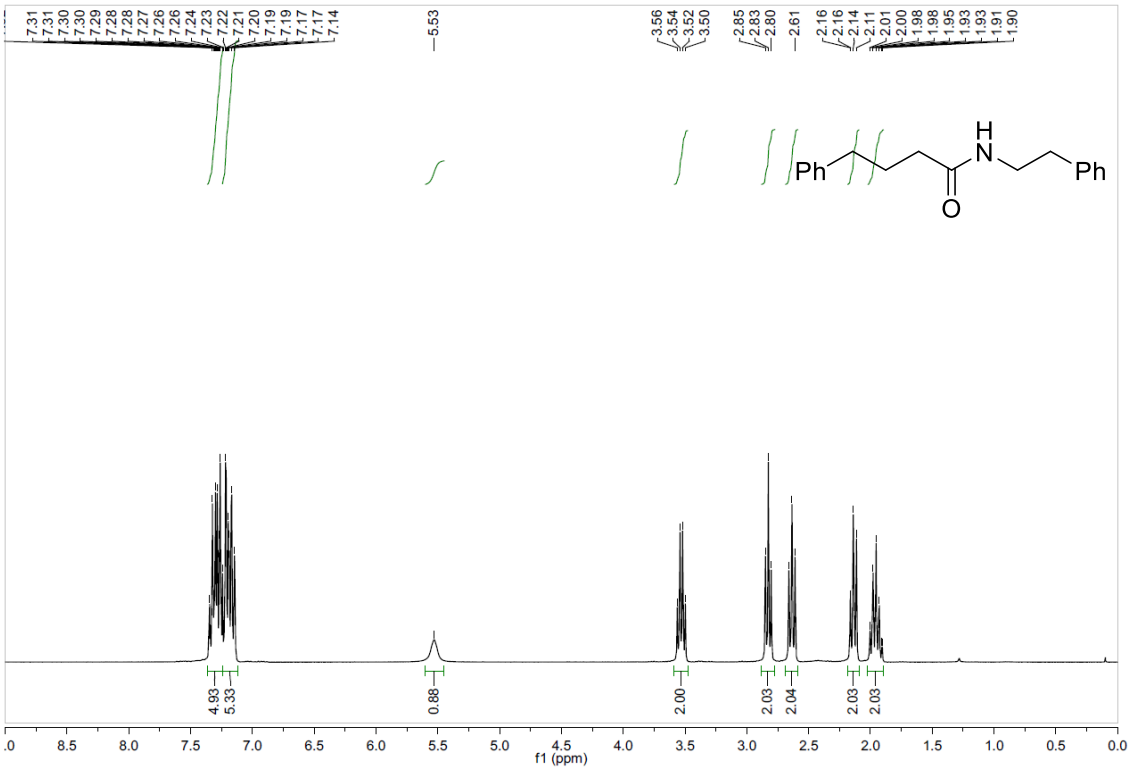
^{1}H NMR (**6g**) ($CDCl_3$)



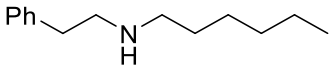
^{13}C NMR (**6g**) ($CDCl_3$)

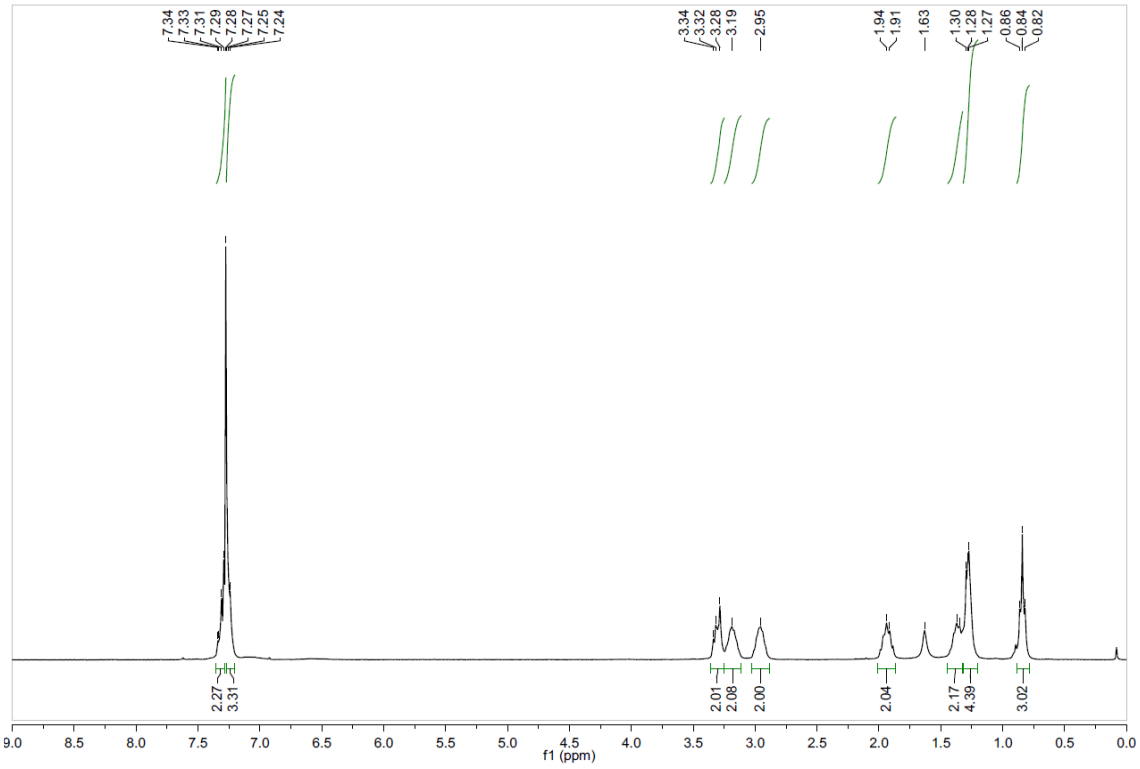


^{1}H NMR (**5h**) ($CDCl_3$)



^{1}H NMR (**6i**) ($CDCl_3$)





국문초록

루테늄과 이리늄 촉매를 이용한 알코올의 촉매적 활성화를 통한 아마이드와 아민의 합성

본 연구는 전이금속 촉매를 이용하여 알코올을 활성화시켜 원자경제적으로 새로운 탄소-질소 결합을 형성하는 반응법에 대한 연구이다. 이것에 기반하여 특히, 유기합성적으로나 산업적으로 매우 유용하게 사용되고 있는 아마이드와 아민의 합성법에 대한 연구를 다루고 있다.

1장에서는 알코올 활성화 방법의 중요성에 대한 내용과 알코올의 활성화를 반응법 개발에 이용한 예들의 선 연구에 대해 소개한다. 2장에서는 알코올 활성화 전략을 기반으로 새로운 질소원인 아자이드와 알코올을 이용하여 아마이드를 합성하는 효율적인 반응법을 개발한 연구를 소개한다. 아마이드를 합성하는 데 있어서 안정하고 다루기 쉬우며 손쉽게 얻을 수 있는 출발물질을 사용하는 것이 매우 중요하다. 본 연구자가 개발한 방법은 아자이드와 알코올을 이용하여 아마이드를 합성해내는 첫번째 반응법이며 이때 개발한 루테늄 촉매 시스템을 이용하여 알코올의 탈수소화와 아자이드의 환원이 이루어진다. 3장에서는 에스터와 일차 아민을 출발 물질로 하여 쉽게 구매할 수 있는 이리듐 촉매하에 아마이드와 이차 아민을 합성해 내는 방법을

처음으로 보고하였다. 두 종류의 중요한 탄소-질소 결합이 한 반응 용기내에서 순차적으로 형성될 수 있었고 이 때 아마이드 결합 형성과 수소 주고-받기 반응법이 순차적으로 이루어졌다. 이 방법은 에스터 작용기를 매우 효율적으로 이용하는 반응법으로써 질소의 공격으로 아마이드가 형성된 후 떨어져나간 알코올을 추가적 탈수소화를 통한 이차 아민의 합성에 이용하게 된다. 이 반응의 결과로 수소와 물 분자만을 부산물로 내어놓게 되므로 청정한 반응이라 할 수 있다. 이렇게 개발된 방법을 통해 아마이드와 아민의 형성 반응법의 새로운 가능성에 기여할 수 있었다.

주요어: 알코올 활성화, 탈수소화, 수소 주고-받기 반응, 전이금속촉매, 탄소-질소 형성반응

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